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Oncogenic Transformation

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

TRANSFORMATION GENE STRUCTURE

1. THREE DIFFERENT HUMAN TUMOR CELL LINES CONTAIN DIFFERENT ONCOGENES.

Murray MJ, Shilo BZ, Shih C, Cowing D, Hsu HW, Weinberg RA
Center Cancer Res., Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA, 02139
Cell; 25(2):355-361 1981

We have obtained foci of transformed mouse cells after transfection of human DNA from colon and bladder carcinoma cell lines and a promyelocytic leukemia cell line. These foci can be shown to contain a large number of human DNA sequences by use of highly repetitive human DNA sequence pro bes. Cell DNA from primary foci can be used in a subsequent cycle of transfection resulting in secondary foci that contain relatively little human DNA. Secondary foci appear to contain only the human sequences proximal to those responsible for the transformed phenotype. A set of characteristic DNA restriction fragments is found in common among secondary foci derived from each tumor cell line DNA. Comparison of the common DNA fragments found in secondary foci derived from three different human tumor cell lines indicates that these three cell lines contain three different transforming genes. (Author abstract) (32 Refs)

2. ACTIVATION OF RELATED TRANSFORMING GENES IN MOUSE AND HUMAN MAMMARY CARCINOMAS (MEETING ABSTRACT).

Lane MA, Sainten A, Cooper GM
Department of Pathology, Sidney Farber Cancer Institute, Boston, MA, 02115
RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 294 pp., 1981.

High mol wt DNAs of five mouse mammary tumor virus (MMTV)-induced tumors, two chemical carcinogen-induced mouse mammary tumors, and one human mammary tumor cell line (MCF-7) were assayed for the presence of transmissible activated transforming genes by transfection of NIH 3T3 mouse cells. DNAs of all 5 MMTV-induced tumors, one chemical carcinogen-induced tumor, and the human tumor cell line induced transformation with high efficiencies. NIH cells transformed by DNAs of MMTV-induced tumors did not contain exogenous MMTV DNA sequences, indicating that MMTV-induced mammary carcinomas contained activated cellular transforming genes that were not linked to viral DNA, NIH cells transformed by DNA of the human tumor cell line contained human DNA sequences detectable by hybridization with human repetitive DNA. The transforming activities of DNAs of all five MMTV-induced tumors, the chemical carcinogen-induced mouse tumor, and the human tumor cell line were inactivated by digestion with the restriction endonucleases Pvu II and Sac I, but not by Bam HI, Eco RI, Hind III, Kpn I or Xho I. These results indicate that the same or closely related transforming genes were activated in six different mouse mammary carcinomas, induced by either MMTV or a chemical carcinogen, and in a humam mammary carcinoma cell line. (no Refs)

3. THE P21 SRC GENES OF HARVEY AND KIRSTEN SARCOMA VIRUSES ORIGINATE FROM DIVERGENT MEMBERS OF A FAMILY OF NORMAL VERTEBRATE GENES.

Ellis RW, DeFeo D, Shih TY, Gonda MA, Young HA, Tsuchida N, Lowy DR, Scolnick EM
Lab. Tumor Virus Genetics, NCI, Bethesda, MD, 20205
Nature; 292(5823):506-511 1981

The Harvey and Kirsten strains of murine sarcoma virus encode enzymatically and serologically related p21 src proteins which are required for virally mediated cellular transformation. The genes in each virus encoding p21 show such extensive divergence from each other that cloned probes from these genes detect distinct sets of cellular genes in the DNA from several vertebrate species. These data suggest that cellular p21 sarc genes constitute a divergent family of vertebrate genes that can regulate the growth of cells. (Author abstract) (39 Refs)

4. TWO DISTINCT CANDIDATE TRANSFORMING GENES OF LYMPHOID LEUKOSIS VIRUS-INDUCED NEOPLASMS.

Cooper GM, Neiman PE
Sidney Farber Cancer Inst., Harvard Medical Sch., Boston, MA, 02115
Nature (Lond); 292(5826):857-858 1981

Further analysis of the avian lymphoid leukosis virus (LLV)-induced tumors used as DNA donors in transfection experiments with NIH 3T3 mouse cells confirmed that the tumors contained exogenous DNA long terminal redundancy (LTR) sequences near the cellular gene (c-myc) homologous to the presumptive transforming gene of myelocytomatosis virus strain MC29. However, chicken c-myc sequences were not detected in NIH 3T3 cells transformed by the DNAs of LLV-induced bursal tumors or a virus-induced lymphoma. These results suggested that LLV-induced tumors contain at least two genes with potential oncogenic activity: a c-myc gene activated by integration of a viral LTR and a distinct cellular gene capable of transforming NIH 373 cells. (12 Refs)

5. A ROUS SARCOMA VIRUS PROVIRUS IS FLANKED BY SHORT DIRECT REPEATS OF A CELLULAR DNA SEQUENCE PRESENT IN ONLY ONE COPY PRIOR TO INTEGRATION.

Hughes SH, Mutschler A, Bishop JM, Varmus HE
Cold Spring Harbor Lab., Cold Spring Harbor, NY, 11724
Proc Natl Acad Sci USA; 78(7,part2):4299-4303 1981

The Rous sarcoma virus (RSV)-transformed rat cell line RSV-NRK-2 contains a single complete RSV provirus. We have obtained recombinant lambda clones that contain both ends of the RSV provirus and the flanking rat sequences. The provirus is integrated in unique DNA and is present in only one of the two homologous chromosomes. The rat sequences into which the RSV provirus integrated were also cloned from the RSV-NRK-2 cell line. The sequences of the regions involved in the recombination event have been determined and compared. Our data suggest that, compared with the sequence of viral DNA in the large circular form of unintegrated viral DNA, the provirus lacks two base pairs at each end and that the provirus is flanked by a six-base-pair direct repeat of cellular DNA. This six-base-pair repeat was apparently created during the integration event because this sequence was present only once at the integration site before the provirus was inserted. A survey of eight other independent RSV transformed rat cell lines demonstrates that, in agreement with earlier results, the RSV proviruses have entered different segments of rat cell DNA. We have also determined the sequence of a second virus DNA-host cell DNA junction from a second RSV-transformed rat cell line (RSV-NRK-4) and find that there are no obvious similarities between the two integration sites or between the integration sites and the termini of viral DNA. (Author abstract) (32 Refs)

6. RECOMBINANT BACTERIOPHAGES CONTAINING THE INTEGRATED TRANSFORMING PROVIRUS OF GARDNER-ARNSTEIN FELINE SARCOMA VIRUS.

Fedele LA, Even J, Garon CF, Donner L, Sherr CJ
Viral Pathology Section, NCI, Bethesda, MD, 20205
Proc Natl Acad Sci USA; 78(7,part2):4036-4040 1981

The integrated DNA provirus of the Gardner-Arnstein (GA) strain of feline sarcoma virus (FeSV) was molecularly cloned in a bacteriophage lambda vector. The cloned DNA fragment is 14.4 kilobase pairs long and contains a 6.7-kilobase provirus flanked by cellular sequences derived from nonproductively transformed mink cells. Transfection of mouse NIH/3T3 cells with the cloned DNA fragment induced foci of transformation at efficiencies of 10(4) focus-forming units/pmol of sarcoma virus DNA. Restriction endonuclease mapping and heteroduplex analyses were used to compare the GA-FeSV provirus with that of Snyder-Theilen (ST)-FeSV, a second strain that contains homologous transformation-specific sequences (v-fes). Both viruses have the general structure 5'-gag-fes-env-c region-3', each having retained portions of the feline leukemia virus (FeLV) gag and env genes. In addition to segments shared by the two sarcoma viruses, GA-FeSV contains 1.7 kilobases of extra sequences not found in ST-FeSV. Of these, at least 400-500 base pairs located near the 5' end of v-fes encode a portion of the GA-FeSV polyprotein; the remaining 1.2 kilobases are derived from the FeLV env gene but do not appear to encode any detectable product related to the FeLV envelope glycoprotein. The close homology of the v-fes sequences shows that GA- and ST-FeSV were formed by recombination of FeLV with similar portions of a cat cellular gene (c-fes). (Author abstract) (36 Refs)

7. CLONING AND CHARACTERIZATION OF THE INTEGRATED VIRAL DNA FROM THREE LINES OF SV40-TRANSFORMED MOUSE CELLS.

Clayton CE, Rigby PW
Cancer Res. Campaign, Eukaryotic Molecular Genetics Res. Group, Imperial Coll. Science and Technology, London SW7 2AZ, England
Cell; 25(2):547-559 1981

Recombinant DNA techniques have been used to isolate the integrated viral DNA, together with flanking cellular sequences, from three independently isolated lines of SV40-transformed BALB/c 3T3 cells. We have determined the structures of these cloned segments and their relationships to one another by restriction enzyme mapping, electron microscopic heteroduplex analysis and transfer hybridization experiments. Our data indicate that the structure of the integrated viral DNA is consistent with the idea that integration involves a tandemly repeated intermediate, that extensive amplification and rearrangement of viral and adjacent cellular sequences occurs after integration and that the majority of viral DNA insertions do not contain an intact early transcription unit. The altered templates presumably encode the truncated and super T antigens found in these cells. Either they are interrupted in the middle of the early region, in which case they generally retain the region in which tsA mutations map, or they contain tandem duplications of the tsA region. Further structural analysis will allow the prediction of the precise structures of these unusual T antigens, and the availability of the corresponding templates opens the way to an analysis of the functions of these proteins. (Author abstract) (52 Refs)

8. THE BIOLOGICAL AND BIOCHEMICAL CHARACTERIZATION OF RAT LEUKEMIA VIRUSES AND THEIR ROLE IN THE GENERATION OF RAT SARCOMA VIRUSES.

Lingua JE
University of Southern California, Los Angeles, CA
Diss Abstr Int (B); 41(11):3981-B 1981

Nucleotide sequences that code for type C viruses are present in the DNA of many mammalian species, including rat. The endogenous rat type of C particles, termed 'rat leukemia virus,' are expressed spontaneously in tumors, aging cultures, or are induced by various chemical or physical agents from normal cells. One viral isolate, obtained from a Sprague Dawley rat embryo (SD-RaLV) is more infectious than other previously described rat type C viruses and has been associated with an acceleration in vitro. Furthermore, when transformed virus-productive Sprague Dawley rat embryo cells were cocultivated with certain chemically-transformed cells, stable sarcoma viruses of purely rat origin were produced (RaSV). This dissertation presents a comprehensive study on the unique properties of rat leukemia virus (RaLV) and rat tumor cells that are conducive for the generation of purely rat sarcoma virus. It is concluded that formation of stable rat sarcoma viruses is a complex recombinational event resulting from a series of interactions between the competent and defective virus particles and with the host cellular gene. (no Refs)

TRANSFORMATION GENE EXPRESSION AND REGULATION

9. THE 28 S GENOMIC RNA OF AVIAN SARCOMA VIRUS PRCII CODES FOR THE TRANSFORMATION-SPECIFIC POLYPROTEIN P105.

DeLamarter JF, Neil JC, Ghysdael J, Vogt PK
(c/o Vogt) Dept. Microbiology, Univ. Southern California, Sch. Medicine, 2011 Zonal Ave., Los Angeles, CA, 90033
Virology; 112(2):757-761 1981

We have characterized the genomic RNA of the defective avian sarcoma virus PRCII. Replicating virus which consists of transforming PRCII and a nontransforming but replication-competent helper, PRCII-AV, contains two RNA species. One is identical in size to the 35 S genome of avian leukosis helper viruses. The second component migrates slightly faster than 28 S ribosomal RNA in polyacrylamide gel electrophoresis but cosediments with this RNA in sucrose gradients. In vitro translation across a gradient of velocity-sedimented poly(A)-containing PRCII virion RNA yielded three major proteins. The virion protein precursors Pr76gag and Pr180gag-pol were translated from 35 S RNA, while the transformation-specific polyprotein P105 was translated from 28 S RNA. P105 may be the only protein coded for by the PRCII genome, although this product would not exhaust the coding capacity of 28 S RNA. Whether translated in vitro or immunoprecipitated from transformed cells, P105 was essentially identical as demonstrated by comparative peptide maps. (Author abstract) (25 Refs)

10. MOUSE MAMMARY TUMOR VIRUS-RELATED PROTEINS: ISOLATION AND CHARACTERIZATION OF A UNIQUE GLYCOPROTEIN.

Anderson SJ
The University of Texas Gradurte School, Houston, TX
Diss Abstr Int (B); 41(12):4493-B 1981

Mouse mammary tumor virus (MMTV) contains six major proteins, identified as gp55, gp33, p25, pp20, p12, and p10. Immunoprecipitation of cytoplasmic extracts from MMTV-infected, pulse-labeled cells identified three MMTV core-specific precursor proteins, termed Pr78gag, Pr110gag, and Pr180gag+. Immunoprecipitation of cytoplasmic extracts from pulse-labeled cells with antisera to gp55 identified two envelope-specific proteins, designated gPr76env and gP79env. A glycoprotein of 130,000 mol wt (gP130) was precipitable from the cytoplasm of GR-strain mouse mammary tumor cells by a rabbit antiserum to Gr-strain mouse mammary tumors virus (GR-MMTV). Two dimensional thin layer analysis of 35S-methionine-containing peptides revealed that five of nine gp33 peptides and one of seven gp55 peptides were shared by gP130 and gPr76env. Six of ten p25 peptides and four more core-related peptides were shared by Pr78gag and gP130. Protein gP130 also contained several tryptic peptides not found in gPr76env, or in the core protein precursors Pr78gag, Pr110gag, or Pr180gag-. Both gP130 and a second protein, p30, were found in immunoprecipitates of detergent disrupted isotopically labeled GR-MMTV treated with anti-MMTV serum. Results suggest that antibodies to gP130 in the anti-MMTV serum are capable of recognizing those protein sequences which are not related to viral structural proteins. These gP130-unique peptides are evidently host specific. Polyproteins consisting of juxtaposed host- and virus-related protein tracts have been implicated in the process of cell transformation in other mammalian systems. Therefore, gP130 may be instrinsic to the oncogenic potential of MMTV. (no Refs)

11. ON SUPPRESSION OF TUMORIGENICITY IN HYBRID AND CYBRID MOUSE CELLS.

Giguere L, Morais R
Cancer Res. Inst., Univ. California Medical Center, San Francisco, CA
Somatic Cell Genet; 7(4):457-471 1981

An attempt was made to find evidence for a cytoplasmic influence on the suppression of tumorigenicity in mouse cells. Cybrids (THBU cybrids) were constructed between whole tumorigenic mouse mammary cells (BALB/c, cell line C2B2 from line MT29240) and enucleated nontumorigenic cells (BALB/c, cell line THOC from clone A31) bearing complementary (nuclear and cytoplasmic) genetic markers. The cybrids were examined for some parameters of in vitro transformation and for tumorigenic capacity and compared to the parental cells. No genetic complementation occurred between the two in vitro transformed parents (THO from clone A31 and C2B2) that could restore the untransformed phenotype in the hybrid cells. In contrast, a strong suppression of tumorigenicity was observed in these hybrids. The analysis of THBU cybrids suggested that the capacity of C2B2 cells to form tumors in vivo can be significantly reduced following fusion with cytoplasts of nontumorigenic cells. This reduction was insufficiently stable or generalized to be observed when mixtures of cybrid colonies were assayed but, for most of the single cybrid clones analyzed, it was clearly expressed in terms of lower take incidence and/or more extended latent periods. (45 Refs)

EXPERIMENTAL MODULATION OF ONCOGENIC TRANSFORMATION

12. MAMMARY TUMOR VIRUS PROVIRAL DNA IN NORMAL MURINE TISSUE AND NON-VIRALLY INDUCED MAMMARY TUMORS.

Michalides R, Wagenaar E, Groner B, Hynes NE
Antoni van Leeuwenhoekhuis, 1066 CX Amsterdam, The Netherlands
J Virol; 39(2):367-376 1981

The Southern DNA filter transfer technique was used to study the involvement of the endogenous mouse mammary tumor virus (MMTV) in the development of mammary tumors of nonviral etiology. The presence of extra MMTV proviruses in the genomes of these non-virally induced mammary tumors would indicate an integration of the provirus of an activated endogenous MMTV. Acquisition of MMTV proviruses did not seem to be an absolute requirement for the development of hormone or carcinogenically induced mammary tumors in strain BALB/c nor for hormone-induced mammary tumors in mouse strains 020, C57BL, and C3Hf. In some hormone-induced mammary tumors we did observe extra MMTV proviruses in submolar quantities, indicating that reintegration may occasionally occur and that only a part of the tumor cells acquired new MMTV DNA information. Hormone-dependent and -independent primary mammary tumors of the mouse strain GR, which are controlled by the Mtv-2 mammary tumor induction gene, all acquired extra MMTV proviruses. Most of these extra MMTV proviral-DNA-containing fragments appeared present in submolar quantities, suggesting that only part of the tumor cells acquired extra MMTV proviral information. These findings indicate that the initially transformed mammary gland cells of non-virally induced mammary tumors do not necessarily acquire extra MMTV proviral DNA information, in contrast to the MMTV-induced mammary tumors, in which all tumor cells contain extra MMTV DNA information. (Author abstract) (34 Refs)

13. ALTERATIONS TO CONTROLS OF CELLULAR DNA SYNTHESIS BY ADENOVIRUS INFECTION.

Braithwaite AW, Murray JD, Bellett AJ
Dept. Microbiology, John Curtin Sch. Medical Res., Australian Natl. Univ., Canberra, A.C.T., 2601, Australia
J Virol; 39(2):331-340 1981

Human adenovirus type 5 and temperature-sensitive mutants ts36, ts37, and ts125 induced cellular DNA synthesis in quiescent rodent cells at both permissive and nonpermissive temperatures. Cellular DNA synthesis induced by adenovirus type 5 or by serum required protein synthesis for both initiation and continuation, whereas viral DNA synthesis was not dependent upon continued protein synthesis once it was initiated. Both cellular and viral DNA replication was induced in adenovirus type 5-infected cells in the presence of dibutyryl cyclic AMP at concentrations which inhibited induction by serum, which suggested that some of the controls of DNA synthesis in serum-treated and virus-infected cells are different. After adenovirus infection of quiescent cells, there was a decrease in the number of cells with G1 DNA content and an increase in cells with G2 diploid and greater DNA contents. Thus, adenovirus type 5 induces a complete round of cellular DNA replication, but in some cells, it induces a second round without completion of a normal mitosis. These results suggest that adenovirus type 5 is able to alter cell growth cycle controls in a way which may be related to its ability to transform cells. (Author abstract) (32 Refs)

14. TRANSFORMATION WITH SUBGENOMIC FRAGMENTS OF FELINE SARCOMA VIRUS PROVIRAL DNA.

Rosenberg ZF, Sahagan BG, Worley MB, Essex M, Haseltine WA
Dept. Microbiology, Harvard Sch. Public Health, Sidney Farber Cancer Inst., Boston, MA
Virology; 112(2):496-504 1981

Murine fibroblasts can be transformed by subgenomic fragments of feline sarcoma virus (FeSV) proviral DNA generated by BamH-I digestion of DNA of Snyder-Theilen FeSV and FeLV-infected mink cells. The efficiency of transformation of NIH 3T3 cells by BamH-I-treated FeSV proviral DNA was the same as that of untreated FeSV DNA. Focus-forming virus could not be rescued from the BamH-I-digested FeSV DNA-transformed cells. However, DNA from these transformed cells was able to induce transformation in secondary transfection experiments. Analysis of the DNAs from two BamH-I-digested FeSV DNA-transformed clones showed that the transformants contained only the 5' two-thirds of the FeSV provirus. Cells transformed by subgenomic fragments of FeSV DNA produce the 85,000-dalton gag-x protein, but do not express FOCMA. These experiments support the notion that the gag-x protein plays an active role in maintenance of the transformed phenotype. (Author abstract) (32 Refs)

15. CLONING OF A DEFECTIVE POLYOMA DNA MOLECULE WITH REARRANGEMENTS IN THE REGION CODING FOR MIDDLE AND LARGE T ANTIGENS.

Parent C, Bastin M
Departement de Microbiologie, Centre Hospitalier Universitaire, Sherbrooke, Quebec J1H 5N4, Canada
FEBS Lett; 130(2):269-271 1981

To define the sequences of polyoma virus (Py) that are essential for cell transformation, defective Py DNA molecules were cloned in pBR322. The recombinant plasmids were tested for their capacity to transform rat 3T3 cells in culture. DNA from the polyoma virus strain ts-P155 was digested with HindIII and the fragments ligated in the HindIII site of pBR322 with T4 DNA ligase. To screen for defective molecules, the recombinant plasmids were selectively digested, and examined by agarose gel electrophoresis and endonuclease mapping. The Py DNA sequence in fragment df55 was found to be interrupted from approx 88-24 units before the HpaII-4/8 junction and the HindII site in HpaII-6. This deletion left the sequence encoding the small T segment intact but removed approx 1,800 base pairs (bp) from the large T antigen gene and about 530 bp from the middle T antigen gene. An interesting feature was the loss of approx 300 bp from the C-terminal portion of the middle T antigen gene. Transfection of 3T3 cells with df55-containing recombinant plasmids failed to transform cultured cells kept for periods up to 3-4 wk at 39 C. The inability of pHdf55 to transform was ascribed to the absence of a functional middle T antigen. While not excluded, the small T antigen alone was not thought capable of inducing expression of the transformed phenotype. (16 Refs)

16. EFFECTS OF RETINOIDS ON NEOPLASTIC TRANSFORMATION, CELL ADHESION, AND MEMBRANE TOPOGRAPHY OF CULTURED 10T1/2 CELLS.

Bertram JS, Mordan LJ, Blair SJ, Hui S
Dept. Experimental Therapeutics, Roswell Park Memorial Inst., Buffalo, NY, 14263
Ann NY Acad Sci; 359:218-236 1981

The effects of retinoids on cell biology was studied in readily transformable C3H/10T1/2 CL8 cell line of mouse embryo fibroblasts. Included are studies on membranes and membrane interactions (cell/substrate adhesion, cell spreading, surface topography). Retinyl acetate caused a dose-dependent reversible inhibition of neoplastic transformation induced by 3-methylcholanthrene. Similar effect was recorded for retinol and retinaldehyde, while all-trans- and 13-cis-retinoic acids failed to inhibit transformation of 10T1/2 cells. Retinoids had no effect on the growth of established cells after the phenotypic expression of transformation. Analysis of the effect of retinoids on cell/substrate adhesion showed that retinyl acetate induced a dose-dependent decrease in the rate of release of trypsin-treated cells. The synthetic retinoids showed an extremely variable response in the adhesion assay. Retinyl acetate at 0.5 ug/ml increased the cell spreading as evidenced by a threefold increase in upper cell surface area and a pronounced increase in the percent of flattened cells. (29 Refs)

17. THE MODULATING EFFECT OF RETINOIDS AND A TUMOR PROMOTER ON MALIGNANT TRANSFORMATION, SISTER CHROMATID EXCHANGES, AND NA/K ATPASE.

Borek C, Miller RC, Geard CR, Guernsey D, Osmak RS, Rutledge-Freeman M, Ong A, Mason H
Radiological Res. Lab., Dept. Radiology, Cancer Center/Inst. Cancer Res., Coll. Physicians and Surgeons, Columbia Univ., New York, NY, 10032
Ann NY Acad Sci; 359:237-250 1981

The interactions between retinoids and tumor promoting compound 12,O-tetradecanoyl-phorbol 13-acetate (TPA) were studied in mouse heteroploid C3H/10T1/2 cells and in diploid hamster embryo cells. TPA added to the culture medium immediately after irradiation with x-rays (300 rads) enhanced markedly the yield of transformed cells, while incubation with retinoids reduced the transformation rate. Retinoids were able to eliminate in an irreversible manner the promoting effect of TPA. Both retinoids and TPA had a comparatively negligible effect on the frequency of sister chromatid exchange. In both cell lines, retinoids reduced the level of Na/K ATPase, while TPA enhanced activity of the enzyme; simultaneous exposure to retinoids and TPA resulted in the normalization of the enzyme level. (38 Refs)

18. VITAMIN A-INDUCED MODULATION OF THE TRANSFORMED CELL PHENOTYPE IN VITRO.

Dion LD, Gifford GE
Lab. Viral Carcinogenesis, NCI, Bethesda, MD, 20205
Ann NY Acad Sci; 359:389-390 1981

The effects of Vitamin A (VA) on interferon synthesis, on the restoration of density-dependent inhibition of cell proliferation, and on other phenotypic markers of transformation in the L-929 cell line are discussed. Experiments using HeLa cell spinner cultures to characterize the VA-induced inhibition of anchorage-independent growth are described. It was suggested that VA may play a role in maintaining normal growth controls although, perhaps, under very specific conditions. (3 Refs)

19. INFLUENCE OF NONCARCINOGENIC SECONDARY FACTORS ON RADIATION CARCINOGENESIS.

Little JB
Lab. Radiobiology, Harvard Univ., Sch. Public Health, Boston, MA, 02115
Radiat Res; 87(2):240-250 1981

The results of experiments on the role of secondary factors in the expression of radiation-induced malignant transformation and carcinogenesis are reviewed. Experiments with mouse embryo fibroblasts (C3H 10T1/2 and BALB/3T3 cell lines) showed that approx 13 or 8-9 rounds of cell division were required for transformation to be fully expressed in x-irradiated cells. Delay of subcultivation for 24-48 hr resulted in marked decrease of the transformation frequency. Irradiation of cells with 25 rads followed by exposure to nonmutagenic dose of 12-O-tetradecanoyl-phorbol-13-acetate (active ingredient of croton oil) increased the transformation frequency to the level recorded after irradiation with 200-300 rads. Such agents as saccharin and endogenous epidermal growth factor were also shown to promote malignant transformation in vitro. Incubation of irradiated cells with inhibitors of proteolytic enzymes, vitamin A, or vitamin C was shown to inhibit malignant transformation. These findings suggest that the initial radiation-induced alteration may be a reversible epigenetic event involving an alteration in gene expression. Intratracheal instillations of isotonic saline was shown to increase the frequency of lung cancer in irradiated hamsters (36% compared with 2% in animals subjected to irradiation alone). These findings indicate that the effect of noncarcinogenic secondary factors are not restricted to in vitro transformation systems. (38 Refs)

20. EPIGENTIC MECHANISMS OF ACTION OF CARCINOGENIC ORGANOCHLORINE PESTICIDES.

Williams GM
Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
ACS Symp Ser; 160:45-56 1981

Carcinogens may be divided operationally into two groups: (1) Genotoxic agents cause direct genetic damage and are a qualitative hazard. (2) Epigenetic agents do not cause genetic damage. They are a quantitative hazard, causing damage when present in high doses. The organochlorine pesticides apparently are epigenetic carcinogens. In cells derived from the liver, the target organ of organochlorine pesticides, these agents have not produced genetic mutations. Pesticides may act on the cell membrane. Several studies have indicated that they interfere with intercellular communication. Cells with abnormal genotypes then proliferate beyond the normal growth requirements of the tissue in which they occur. The apparent lack of carcinogenic effects in human populations may be due to insufficient exposure, more efficient intercellular communications in humans, or a lack of the genetic alterations in the liver necessary to give rise to neoplasms in the presence of a promoting agent. (45 Refs)

21. TUMOR PROMOTING AGENTS.

Tsilimigras CW
Natl. Inst. for Virology, Private Bag X4, Sandringham, Johannesburg 2131, South Africa
S Afr J Sci; 77(3):100-103 1981

The effects of tumor promoting agents, particularly the phorbol ester 12-O-tetradecanoyl-phorbol-13-acetate (TPA) on cells in vitro are considered. The major diterpene ester of croton oil, TPA has been shown to be the most potent promoter of multiple skin tumors in vivo. It has also been found to induce many different responses in vitro, including enhancement of transformation, stimulation of a number of specific enzymes and cyclic nucleotides, modifications in macronucleotides, modifications in macromolecular synthesis, an inhibition of terminal differentiation, changes in cellular membranes and cellular morphology, and disturbances of the transport of cations and small molecules through membranes. TPA has been reported to enhance the degree of the in vitro transformation of fibroblast cell cultures and rat embryo cells previously exposed to polycyclic aromatic hydrocarbons, UV light, or adenoviruses. TPA has also been found to enhance the expression of transformation by Rous sarcoma virus in chick embryo fibroblasts. TPA had been shown to induce ornithine decarboxylase, protease, and plasminogen activator. TPA seems to stimulate DNA and RNA synthesis. Other classes of possible tumor promoters, such as melittin, phenol, oleic acid, some non-aromatic hydrocarbons, Tween 60, saccharin, and cyclamate, are discussed. (16 Refs)

22. INDUCTION OF TRANSFORMED PHENOTYPES IN SHEEP FIBROBLASTS BY CULTURE FLUIDS FROM CELLS PERSISTENTLY INFECTED WITH BOVINE LEUKEMIA VIRUS.

Onuma M, Watarai S, Suneya M, Mikami T, Izawa H
Dept. Epizootiology, Faculty Veterinary Medicine, Hokkaido Univ., Sapporo, Hokkaido 060, Japan
Microbiol Immunol; 25(5):445-454 1981

Transformation of sheep fibroblasts by incubation with culture fluids from bovine leukemia virus (BLV)-producing fetal lamb kidney (FLK) cells and calf-born bovine lymphosarcoma (3178) cells is reported. Inoculation of concentrated culture fluids from FLK and 3178 cells onto fibroblasts from testes of normal sheep produced a morphological transformation from fibroblast-like to epithelial-like cells; the changes were observed after the second or third passage. Syncytial assay showed the presence of BLV in all transformed cells, and electron microscopy revealed the presence of type C virus. Transplantation of virus-infected sheep fibroblasts produced tumor growth in athymic nude mice; the tumors had histology of fibrosarcoma. Transformed cells showed a 2.8-3.5x greater uptake of the glucose analog (2-deoxy-D-glucose) than control sheep fibroblasts. (24 Refs)

BIOCHEMICAL AND MOLECULAR BIOLOGICAL STUDIES OF TRANSFORMED PHENOTYPE

23. PURIFIED LOW-MOLECULAR-WEIGHT PROTEIN KINASE FROM MURINE SARCOMA VIRUS PARTICLES CATALYZES TYROSINE PHOSPHORYLATION ENDOGENOUSLY BUT PHOSPHORYLATES CELLULAR PROTEINS AT SERINE.

Sen A
Dept. Cellular Biology, Scripps Clinic and Res. Foundation, La Jolla, CA, 92037
J Virol; 39(2):612-624 1981

The low-mol-wt (LMW) protein kinase associated with high-titer murine sarcoma virions has been extensively purified by ammonium sulfate fractionation, Bio-Gel P-100 gel filtration, DEAE-cellulose and carboxymethyl cellulose chromatography. The purified enzyme migrates as a 16K polypeptide in polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulfate. The enzyme catalyzes phosphotransfer with ATP as a phosphate donor to various exogenously added proteins as acceptors; it requires Mg++ and is independent of cyclic AMP. The enzyme preparation catalyzes a low level of phosphorylation in the absence of any exogenously added substrate and forms phosphotyrosine. However, in the presence of acceptor protein molecules including total soluble cytoplasmic proteins of murine sarcoma virus-transformed mouse cells, the phosphorylated end products contain predominantly phosphoserine. The virion-associated enzyme also shows a preference for phosphorylating certain polypeptides in the soluble cytoplasmic extracts of murine sarcoma virus-transformed cells. (Author abstract) (24 Refs)

24. THE SPECIFIC INTERACTION OF THE ROUS SARCOMA VIRUS TRANSFORMING PROTEIN, PP60SRC, WITH TWO CELLULAR PROTEINS.

Brugge JS, Erikson E, Erikson RL
Dept. Microbiology, Sch. Medicine, State Univ. New York, Stony Brook, Long Island, NY, 11794
Cell; 25(2):363-372 1981

Sera from rabbits bearing tumors induced by Rous sarcoma virus (RSV) were previously found to contain antibody to the RSV transforming protein, pp60src. Two additional transformation-specific phosphoproteins from RSV-transformed avian cells are immunoprecipitated with these sera. These proteins, having mol wt of 90,000 (pp90) and 50,000 (pp50), are not precipitated from uninfected or transformation-defective virus-infected cells and are not related to any RSV structural proteins. Normal uninfected chicken cells contain a protein that shares identical partial proteolytic cleavage peptides with the pp90 protein immunoprecipitated from RSV-transformed cells. This pp90 protein is one of the major cytoplasmic proteins in uninfected cells. Antibody directed against pp90 also immunoprecipitates pp60src and pp50 from lysates of RSV-transformed chicken cells. (Author abstract) (33 Refs)

25. PHOSPHORYLATION OF RIBOSOMAL PROTEIN S6 IN AVIAN SARCOMA VIRUS-TRANSFORMED CHICKEN EMBRYO FIBROBLASTS.

Decker S
Rockefeller Univ., 1230 York Ave., New York, NY, 10021
Proc Natl Acad Sci USA; 78(7,part2):4112-4115 1981

Protein phosphorylation was examined in whole cell extracts from normal and avian sarcoma virus-transformed chicken embryo fibroblasts. The addition of serum or epidermal growth factor to serum-starved normal cells resulted in increased 32P labeling of a Mr 30,000 protein. In extracts from cells transformed by a temperature-sensitive mutant of Schmidt-Ruppin virus, subgroup A, and grown at the permissive temperature, the protein was phosphorylated regardless of serum starvation. This Mr 30,000 protein was shown to be ribosomal protein S6, and the effects of avian sarcoma virus transformation on S6 phosphorylation were further investigated. The ability to phosphorylate S6 in the absence of serum was found to be temperature sensitive when S6 preparations from the temperature-sensitive mutant-infected cells incubated at permissive and nonpermissive temperatures were compared. Cells transformed by the parent virus (Schmidt-Ruppin, subgroup A) maintained the ability to phosphorylate S6 in the absence of serum when incubated at either temperature. Phosphoserine was the only phospho-amino acid detected in acid hydrolysates from phosphorylated S6 preparations. (Author abstract) (20 Refs)

26. CYCLIC AMP-DEPENDENT PROTEIN KINASES FROM BALB 3T3 CELLS AND OTHER 3T3 DERIVED LINES.

Wehner JM, Malkinson AM, Wiser MF, Sheppard JR
Dept. Genetics and Cell Biology, Univ. Minnesota, Minneapolis, MN, 55455
J Cell Physiol; 108(2):175-184 1981

Cyclic AMP-dependent protein kinase and 3H-cyclic AMP (3H-cAMP) binding activities were compared in normal Balb 3T3 cells and SV40, chemical, and spontaneous transformants of Balb 3T3. The photoaffinity analogue of cAMP, 8-N3 cAMP, was used to measure the amounts of R-I and R-II of protein kinase subunits in sonicates obtained from cells. Analysis of protein kinase activities showed no significant differences among normal and transformed cell types. The normal 3T3 cells prepared by homogenization showed lower soluble 3H-cAMP-binding activity than the transformed strains, but higher particulate activity. Apparently the method of cell disruption affected 3H-cAMP-binding activity in 3T3 cells, but not in transformed cells. Diethylaminoethanol chromatography showed that 3T3 cells contained only R-II isozymes. The transformed cells contained both R-I and R-II isozymes. Cells from rat kidney, chicken embryo, and human and calf endothelial tissue also contained both isozymes. The 8-N3 cAMP-binding confirmed that transformed cells have much more R-I than normal 3T3 cells. Evidently the 3T3 cells were derived from embryonic precursors of adipocytes and have retained a characteristic adipocyte isozyme pattern in culture. (37 Refs)

27. TRANSFORMATION-ENHANCING FACTOR(S) RELEASED FROM CHICKEN ROUS SARCOMA CELLS: EFFECT ON SOME TRANSFORMATION PARAMETERS.

Kryceve-Martinerie C, Biquard JM, Lawrence D, Vigier P, Barlati S, Mignatti P
Faculte des Sciences, Institut Curie (Biologie), 91405 Orsay, France
Virology; 112(2):436-449 1981

The medium of chick embryo fibroblasts (CEF) transformed by Schmidt-Ruppin strain of Rous sarcoma virus (SR-RSV) contains a factor(s) which complements the expression of some transformation parameters depending on the src gene. Notably, it reverses the block by puromycin of morphological transformation of cells infected with three ts-T mutants after shift-down from restrictive (41.5 C) to permissive (37 C) temperature. This reversal is not due to the release of inhibition of protein synthesis produced by puromycin, and is accompanied by the expression of two other src-dependent transformation parameters: disorganization of the cytoskeleton and loss of cell surface-associated fibronectin. The factor(s) able to overcome the puromycin block of morphological transformation was operationally called transformation-enhancing factor (TEF) like a previously reported factor favoring transformation by RSV. It is lacking in media of untransformed cells, uninfected or infected with a nontransforming virus (RAV-1), and its production by RSV-infected cells seems to depend on the acquisition of the transformed phenotype, therefore on the expression of the src gene. Its effect was also shown to persist beyond the period of contact with the cells. It appears to be a glycoprotein which can be resolved by gel filtration into two peaks of 250K and 190K, apparently distinct from other known factors spontaneously released by transformed cells. A similar activity was also found in the medium of mammalian (rodent) cells transformed by SR-RSV and by other RNA and DNA oncogenic viruses, but not in the medium of untransformed controls. (Author abstract) (38 Refs)

28. REGULATION OF PASSIVE POTASSIUM TRANSPORT OF NORMAL AND TRANSFORMED 3T3 MOUSE CELL CULTURES BY EXTERNAL CALCIUM CONCENTRATION AND TEMPERATURE.

Ernst M, Adam G
Max Planck Institut fur Immunbiologie, Stubeweg 51, D-7800 Freiburg, W. Germany
J Membr Biol; 61(3):155-172 1981

Regulation of passive potassium ion transport by the external calcium concentration and temperature was studied on cell cultures of 3T3 mouse cells and their DNA-virus transformed derivatives. Upon lowering of external calcium concentration, passive potassium efflux generally exhibits a sharp increase at about 0.1 mM. The fraction of calcium-regulated potassium efflux is largely independent of temperature in the cases of the transformed cells, but shows a sharp increase for 3T3 cells upon increasing temperature above 32 C. In the same range of temperature, the 3T3 cells exhibit the phenomenon of high-temperature inactivation of the residual potassium efflux at 1 mM external calcium. At comparable cellular growth densities, the transformed cell lines do not show high-temperature inactivation of 'residual' K efflux. These results are consistent with the notion of a decisive role of the internal $K+$ concentration in the cell-density dependent regulation of cell proliferation. In particular, the growth-inhibiting effect of lowering the external $Ca++$ concentrations is considered as largely due to a rise of passive $K+$ efflux and a subsequent decrease of internal $K+$ concentration. The experimental data on the $Ca++$ dependence of passive $K+$ flux are quantitatively described by a theoretical model based on the constant field relations including negative surface charges on the external face of the membrane, which cooperatively bind $Ca++$ ions and may concomitantly undergo a lateral redistribution. The present evidence is consistent with acidic phospholipids as representing these negative surface charges. (Author abstract) (111 Refs)

29. AVIAN RETICULOENDOTHELIOSIS VIRUS: IDENTIFICATION OF THE HEMATOPOIETIC TARGET CELL FOR TRANSFORMATION.

Lewis RB, McClure J, Rup B, Niesel DW, Garry RF, Hoelzer JD, Nazerian K, Bose HR
Dept. Microbiology, Univ. Texas, Austin, TX, 78712
Cell; 25(2):421-431 1981

Non-virus-producing hematopoietic cells transformed in vitro by reticuloendotheliosis virus (REV-T) induced lethal 'reticuloendotheliosis' when inoculated into histocompatible chickens. This is the first direct demonstration that an in vivo target cell of an avian acute leukemia virus can be transformed in vitro. The tumorigenic, REV-T-transformed non-virus-producing cells fail to express helper-virus-coded proteins. REV-T-transformed tumorigenic cells therefore do not require helper-virus functions. Cells transformed in vivo or in vitro by REV-T have lymphoblastoid morphology and express low levels of terminal-deoxynucleotidyl-transferase activity and bursal-cell determinants. One clone synthesized Ig u. The preferred target cells for REV-T transformation are therefore immature lymphoid cells that express B-cell determinants. We propose that the unique transforming sequence of REV-T be designated rel (lymphoid). (Author abstract) (56 Refs)

CELL SURFACE PHENOMENA OF TRANSFORMATION

30. IMMUNOLOGIC DISSECTION OF THE ANTIGENIC SPECIFICITY INDUCED BY ROUS SARCOMA VIRUS BY MEANS OF MONOCLONAL ANTIBODIES (MEETING ABSTRACT).

Ferracini R, Comoglio PM
Istituto di Anatomia Umana, Universita di Torino, Turin, Italy
Tumori; 67(2,SupplA):167 1981

Rous sarcoma virus (RSV)-transformed mammalian fibroblasts express a membrane antigen (VCSA) controlled by transforming gene src, the viral genome segment directly responsible for the induction and maintenance of neoplastic transformation. By cloning somatic hybrids of murine myeloma lines with splenic lymphocytes from mice hyperimmunized with RSV-transformed cells, it has been possible to produce a certain number of monoclonal antibodies directed against this antigen. Binding tests between selected monoclonal antibodies and a series of cells from different animal species transformed by RSV have made it possible to show that the VCSA antigen is the result of the combined expression on the cell surface of various antigenic determinants controlled either by host cell genes or viral src genes. It is concluded that the expression of VCSA antigen is not due to the insertion of an individual viral protein on the cell surface, but is the result of a change induced by the product of the src gene on one or more components of the plasma membrane coded by cellular genes. (1 Ref) (In ITA)

31. VIRAL SRC GENE AND CELLULAR GENES INTERACTING IN THE EXPRESSION OF ROUS SARCOMA VIRUS (RSV)-INDUCED TRANSFORMATION AND TRANSPLANTATION CELL SURFACE ANTIGENS (MEETING ABSTRACT).

Prat M, Tarone G, Comoglio PM
Department of Histology, University of Trieste, School of Medicine, Trieste, Italy
Immunobiol; 159(1/2):189 1981

Avian and mammalian fibroblasts transformed by RSV express a serologically detectable virus-induced non-virion cell surface antigen (VCSA), whose expression is controlled by the transforming viral src gene. By inhibition experiments performed with cytotoxic antibodies and RSV-transformed cells of different animal species, it has been found that VCSA expression on transformed hamster fibroblasts is a complex of two antigenic specificities, one controlled by the viral genome and one controlled by the host cellular genome. By in-vivo immunization we have now found that RSV-transformed fibroblasts from different mouse strains share a virus-specific transplantation antigen. Immunoprecipitation tests with mono-specific antisera showed that the expression of this antigen does not correlate with the presence of intracellular viral proteins other than the src gene product pp60src. However, hyperimmunization of mice with hamster or quail fibroblasts transformed by RSV that express a high level of pp60src did not induce transplantation resistance. It is concluded that the expression of the serologically-defined VCSA and the transplantation antigen is the result of the interaction of pp60src with host cell gene product(s) rather than the simple exposure of pp60src at the outer cell surface. (no Refs)

32. PREPARATION OF AUTOLOGOUS ANTISERUM AGAINST SSV NONPRODUCER CELLS AND ITS PARTIAL CHARACTERIZATION.

Thiel HJ, Iglehart JD, Matthews TJ, Broughton EM

Bundesforschungsanstalt fur Viruskrankheiten der Tiere, P.O. Box 1149, Paul-Ehrlich-Str. 28, 7400 Tubingen, W. Germany

Virology; 112(2):634-641 1981

In order to prepare an autologous antiserum against SSV nonproducer cells (SSV-NP cells), goat fibroblasts from a biopsy specimen were infected with SSV (SSAV) and transformed nonproducer clones were isolated. One of these clones was propagated in autologous goat serum and inoculated into the same goat. Characterization of the resulting antiserum by a surface specific binding assay showed specific reactivity with NRK-SSV nonproducer cells which cannot be adsorbed by an SSAV virus resin. The data suggest that the serum recognizes cell surface molecules, which might be specific for transformation by SSV. (Author abstract) (16 Refs)

MORPHOLOGICAL AND OTHER BIOLOGICAL ASPECTS OF ONCOGENIC TRANSFORMATION

33. CHROMOSOME ANALYSES AND ANCHORAGE-INDEPENDENT GROWTH OF SV40-INDUCED MORPHOLOGICALLY TRANSFORMED EPITHELIAL CELLS FROM AMNIOTIC FLUIDS.

Walen KH

Viral and Rickettsial Disease Lab., California State Dept. Health Services, 2151 Berkeley Way, Berkeley, CA, 94704

In Vitro; 17(6):531-539 1981

Epithelial cells from amniotic fluid cell cultures are morphologically transformed by simian virus 40, 20 to 30 days after infection. The cells of the transformed colonies are highly basoph ilic, have a high nuclear-to-cytoplasmic ratio, and show a dense growth pattern. The cells are virus producers, and ultimately, after continuous passage, the cell lines reach a crisis situation with no growth. Twelve morphologically transformed cell colonies were isolated from five different individuals for chromosome analyses after approx 18 population doublings (2nd bottle passage). For all cell lines diploid cells were observed. Banding of the chromosomes revealed normal morphology of euchromatic and heterochromatic regions. The suggestion is made that chromosome alteration is not necessary, nor a prerequisite, for the morphologically transformed phenotype to be expressed and that the transformation process per se causes chromosomal instability. Tests for colony formation of the 12 cell lines in semisolid medium showed that different transformed colony isolates from the same individual donor of the cells either formed or did not form colonies in agar. The size of the colonies was also consistent within individuals as compared to between individuals. These limited results are suggestive of a dependence upon the genetic constitution of the individual donor of the cells for colony formation in soft agar. (Author abstract) (33 Refs)

34. BASAL LAMINA FORMATION BY NORMAL AND TRANSFORMED MOUSE MAMMARY EPITHELIAL CELLS DUPLICATED IN VITRO.

David G, Van der Schueren B, Bernfield M

(c/o Bernfield) Dept. Pediatrics, Stanford Univ. Sch. Medicine, Stanford, CA, 94305

JNCI; 67(3):719-728 1981

Cells from low-passage (LP) cultures of a mouse mammary epithelial line (NMuMG cells) form a basal lamina when they are cultured on a Type I collagen gel substratum. A high-passage (HP) strain of this line maintained the morphologic, serologic, and karyologic properties of the LP cells. For the determination of whether transformation of the NMuMG cells might lead to defects in the basal lamina, cells from LP cultures were compared in vivo and in vitro with cells of HP cultures for tumorigenicity, growth characteristics, and ability to form a lamina. The LP NMuMG cells had a typical epithelial morphology and showed no cytologic evidence of cancer. They formed an ultrastructurally normal continuous basal lamina in vivo when they were injected into athymic nude mice. In contrast, the HP cells were pleomorphic and highly invasive when injected into nude mice where they showed frequent and large basal lamina defects. These cells also accumulated only traces of lamina-like materials when cultured on a collagen gel, indicating that neoplastic transformation had markedly reduced the ability of NMuMG cells to form a basal lamina both in vivo and in vitro. Because the collagen gel culture system duplicated the in vivo situation with regard to basal lamina integrity, the basis for this lack of in vitro basal lamina formation may be physiologically relevant for the mechanism of malignant invasion. (Author abstract) (33 Refs)

35. VARIATIONS IN THE NUCLEAR-CYTOPLASMIC RATIO DURING EPITHELIAL DIFFERENTIATION IN EXPERIMENTAL ORAL CARCINOGENESIS.

White FH, Gohari K

Dept. Human Biology and Anatomy, Univ. Sheffield, Western Bank, Sheffield S10 2TN, England

J Oral Pathol; 10(3):164-172 1981

Alterations in the ratio of nucleus to cytoplasm (N/C ratio) at the ultrastructural level during experimental carcinogenesis in the hamster cheek pouch epithelium quantified in order to assess whether the N/C ratio could be used to indicate premalignancy and malignant transformation. During differentiation, all experimental stages showed a marked tendency for N/C to decrease progressively between basal and granular layers. These decreases were significant in the normal and in the preneoplastic groups, but not significant between the basal and spinous layers in the carcinoma group. During carcinogenesis, the N/C ratios at each cellular layer tended to increase between normal and carcinoma stages. Significant differences were detected in the spinous and granular layers: the larger difference between normal and carcinoma layers was found in the spinous layer and smallest in the basal layer. These results suggest that, while increases in the N/C ratio are a feature of malignant progression, these increases are not uniform at the ultrastructural level for each of the epithelial compartments. It was concluded that the N/C ratio is not a useful ultrastructural discriminant for the detection of premalignancy which is undetected by conventional histological assessment. (35 Refs)

36. INITIATION POINTS FOR CELLULAR DEOXYRIBONUCLEIC ACID REPLICATION IN HUMAN LYMPHOID CELLS CONVERTED BY EPSTEIN-BARR VIRUS.

Oppenheim A, Shlomai Z, Ben-Bassat H
NCI, Bethesda, MD, 20205
Mol Cell Biol; 1(8):753-762 1981

Replicon size of two Epstein-Barr virus (EBV)-negative lymphoma cell lines, BJAB and Ramos, was measured, as in each of these lines converted by two strains of EBV, derived from the producer cell lines B95-8 and P3HR-1. Logarithmic cultures of randomly growing cells were labeled for 8 min with high-specific activity [3H]thymidine, the cells were gently lysed, and the DNA was spread on microscope slides and autoradiographed. In this manner, replication forks can be observed along the DNA fiber that became labeled during the radioactive pulse. Av replicon length was measured. Significantly shorter replicons (41, 21, and 54% shorter, respectively) were found in three of the four EBV-converted cell lines, BJAB/B95-8, Ra/B95-8, and Ra/HRIK, indicating that these cells had more initiation points than their EBV-negative parents. Replicons that were only slightly shorter than those of the parents were found in BJAB/HRIK cells, although extensive track fusion occurred during the labeling of BJAB/HRIK. This implies that the true av replicon size of these cells was shorter than the observed value. It is suggested that EBV activates new initiation points for cellular DNA replication in EBV-transformed cells (27 Refs)

37. NO ACTIVATION OF NEW INITIATION POINTS FOR DEOXYRIBONUCLEIC ACID REPLICATION IN BALB/C 3T3 CELLS TRANSFORMED BY KIRSTEN SARCOMA VIRUS.

Oppenheim A, Horowitz AT
NCI, Bethesda, MD, 20205
Mol Cell Biol; 1(8):763-768 1981

BALB/c 3T3 cells were transformed with Kirsten sarcoma virus and murine leukemia virus as a helper, and five clones were isolated in soft agar. These transformed cells had rounded, piled-up morphology and grew to higher densities than the nontransformed cells. Fiber-autoradiography on cells at low passage after transformation was performed. Analysis of replicon sizes and intertrack distances conducted. Very little difference in replicon size between the transformed and the nontransformed lines was noted. A more precise analysis was conducted on 3T3 and two of the transformed clones: one with the shortest replicons and one with the longest replicons. The distributions of logs of intertrack distances were assumed to be normal and the distributions of the experimental points for the three cell lines were very close to one another and overlapped extensively. These results suggest that cellular transformation can be established and maintained by several basically different molecular mechanisms, depending on the nature of the transformation protein. (33 Refs)

ASSAYS OF ONCOGENIC TRANSFORMATION

38. MOLECULAR CLONING OF THE AVIAN MYELOCYTOMATOSIS VIRUS GENOME AND RECOVERY OF INFECTIOUS VIRUSES BY TRANSFECTION OF CHICKEN CELLS.

Vennstrom B, Moscovici C, Goodman HM, Bishop JM
Dept. Microbiology, Biomedical Center, Uppsala, Sweden
J Virol; 39(2):625-631 1981

The avian retrovirus myelocytomatosis virus 19 (MCV) possesses an interesting diversity of oncogenic potentials, but the virus has proven difficult to study because of its inability to replicate without the assistance of a helper virus. We have therefore isolated and amplified the genome of MCV by molecular cloning in a prokaryotic vector. The topography of the cloned DNA was explored by the use of restriction endonucleases and radioactive complementary DNAs representing specific domains in avian retrovirus genomes. The cloned DNA appeared to be an authentic representation of the MCV genome: the size and genetic topography of the DNA were comparable to those of MCV, and transfection of the cloned DNA into chicken cells (in company with the DNA of a suitable helper virus) gave rise to virus with the genome and transforming potentials of MCV. The availability of cloned MCV DNA should facilitate a variety of genetic and biochemical manipulations directed at elucidating the mechanism of oncogenesis by MCV. (Author abstract) (25 Refs)

GENERAL REVIEWS AND OTHER RELATED STUDIES

39. TUMOR VIRUSES AS MODIFIERS OF THE NUCLEAR GENOME OF EUKARYOTIC CELLS.

Sheinin R
Dept. Microbiology and Parasitology, Univ. Toronto, Toronto M5S 1A1, Canada
Ann NY Acad Sci; 361:435-460 1981

The mechanism of action of tumor viruses as modifiers of host genome is explored. Tumor viruses have apparently evolved as chromosomal parasites, integrating viral DNA into the genome of host cells. The most successful evolution would produce a viral genome integrated into the DNA of the host's germ cells. Less successful would be a viral genome effective only in specific somatic cells. The mechanism of integration may involve covalently closed, double-stranded DNA genome forms. Optimum evolutionary development would favor a viral genome under the control of the host. Silencing of the viral genome has been avoided by the horizontal transmission required by the life cycle of tumor viruses. Neoplastic conversion of host cells may depend on two determinants: a virogene derived from the virus, and an oncogene present in the cellular genome. Oncogenic DNA-containing viruses evidently carry into the host cell the DNA required for producing tumor antigens and related proteins. Genetic relatedness has been demonstrated among the DNA-containing viruses and among the oncogenic retroviruses. This relatedness is useful in studying the evolution of viruses. It also provides insights into vertebrate relatedness and paleontological origins. (187 Refs)

40. A UNIFIED THEORY OF CARCINOGENESIS: ACTIVATION OF TRANSPOSABLE GENETIC ELEMENTS WITH ONCOGENIC POTENTIAL.

Renan MJ
Div. Radiation Oncology, Dept. Radiology, UCI Medical Center, 101 City Drive South, Orange, CA, 92668

Speculations Sci Technol; 4(1):7-20 1981

In developing a unified theory of carcinogenesis, several theories are critically examined, including the mutation model, viral etiologies, and two-stage and integrative theories. Aspects of viral genetics necessary for exposition of the author's model are discussed. A mechanism for the activation of endogenous sequences in vertebrates is proposed. A unified theory of carcinogenesis is presented. The model is then extended to include human neoplasia, and the 'transformon' theory is introduced. It is suggested that in mammalian and avian systems, endogenous genetic elements with transforming potential are activated when the survival of the host cell is threatened. These sequences may have evolved from recombinant events between retroviral genomes and normal cellular genes. It is proposed that human malignancy results from the activation of a transposable genetic element (or transposon) and the subsequent integration of this DNA segment into the genome of a suitable cell. The designation 'transformon' is suggested for the transposed sequence, which in the simplest model consists of a cellular oncogene, a gene coding for transposase, and a gene encoding a repressor protein. (161 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. THE GENETIC TOXICOLOGY OF ALDRIN AND DIELDRIN.

Ashwood-Smith MJ
Environmental Toxicology Res. Group, Dept. Biology, Univ. Victoria, Victoria, BC V8W 2Y2, Canada
Mutat Res; 86(2):137-154 1981

RADIATION CARCINOGENESIS

2. EFFECTS OF LOW-LEVEL RADIATION ON BIOLOGIC SYSTEMS: A LITERATURE REVIEW.

Best TL, Hoditschek B
Eastern New Mexico Univ., Portales, NM
Effects of Low-Level Radiation on Biologic Systems: A Literature Review. Available from National Technical Information Service, Springfield, VA, as SAND-80-7143:, 246 pp., 1981.

3. PHOTOCARCINOGENESIS: AN OVERVIEW.

Forbes PD
Skin and Cancer Hosp., 3322 North Broad St., Philadelphia, PA, 19140
J Invest Dermatol; 77(1):139-143 1981

DIETARY FACTORS IN CARCINOGENESIS

4. EPIDEMIOLOGICAL CORRELATIONS BETWEEN DIET AND CANCER FREQUENCY.

Correa P
Louisiana State Univ. Medical Center, New Orleans, LA, 70112
Cancer Res; 41(9,part2):3685-3689 1981

5. ROLE OF DIETARY FIBER IN DIVERTICULAR DISEASE AND COLON CANCER.

Talbot JM
Life Sciences Res. Office, Federation of American Societies for Experimental Biology, Bethesda, MD, 20014
Fed Proc; 40(9):2337-2342 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

6. PRIMARY HEPATIC CANCER IN ALCOHOLICS.

Tamburro CH, Lee HM
Liver Res. Center, Div. Digestive Diseases and Nutrition, Univ. Louisville Health Sciences Center, 511 South Floyd St., Louisville, KY, 40232
Clin Gastroenterol; 10(2):457-477 1981

7. PANCREATIC CANCER AND ALCOHOL.

Okuda K, Ohnishi K
Dept. Medicine, Chiba Univ. Sch. Medicine, 1-8-1 Inohana, Chiba City (280), Japan
Clin Gastroenterol; 10(2):479-484 1981

8. HELMINTHS IN THE INDUCTION OF CANCER. II. SCHISTOSOMA HAEMATOBIUM AND BLADDER CANCER.

Schwartz DA
Inst. Medicine, Far Eastern Univ., Manila, Philippines
Trop Geogr Med; 33(1):1-7 1981

9. GENETICS OF WILMS'S TUMOR.

Matsunaga E
Dept. Human Genetics, Natl. Inst. Genetics, Mishima, Shizuoka-Ken, 411, Japan
Hum Genet; 57(3):231-246 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

10. NEOPLASMS: COMPARATIVE PATHOLOGY OF GROWTH IN ANIMALS, PLANTS, AND MAN.

Kaiser HE
Dept. Pathology, Univ. Maryland Sch. Medicine, Baltimore, MD
Neoplasms: Comparative Pathology of Growth in Animals, Plants, and Man. Baltimore, Williams and Wilkins, 908 pp., 1981.

11. PULMONARY CARCINOGENESIS: ARYL HYDROCARBON HYDROXYLASE.

McLemore TL, Martin RR
Dept. Medicine, Baylor Coll. Medicine, Houston, TX, 77030
Cancer Treat Res; 1:1-34 1981

12. THE GENETIC TOXICITY OF HYDROXYLAMINES.

Marfey P, Robinson E
Dept. Biological Sciences, State Univ. New York at Albany, Albany, NY, 12222
Mutat Res; 86(2):155-191 1981

MODIFICATION OF CARCINOGENESIS

13. MODIFYING FACTORS OF CHEMICAL CARCINOGENESIS.

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Laboratoire d'Anatomie Pathologique, Tour de Pathologie B. 23, Universite de Liege au Sart Tilman, 4000 Liege, Belgium
Pathol Res Pract; 171(2):268-278 1981

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Brookes P
(c/o Lohman, P. H.), Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
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Russell ES
Jackson Lab., Bar Harbor, ME, 04609
Prog Clin Biol Res 45: 327 pp., 1981.

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FEBRUARY, 1982

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TRANSFORMATION GENE STRUCTURE

1. ACTIVATION OF RELATED TRANSFORMING GENES IN MOUSE AND HUMAN MAMMARY CARCINOMAS.

Lane MA, Sainten A, Cooper GM
Sidney Farber Cancer Inst., Boston, MA, 02115
Proc Natl Acad Sci USA; 78(8):5185-5189 1981

High mol wt DNAs of five tumors induced by mouse mammary tumor virus (MMTV), two mouse mammary tumors induced by a chemical carcinogen, and one human mammary tumor cell line (MCF-7) were assayed for the presence of transmissible activated transforming genes by transfection of NIH 3T3 mouse cells. DNAs of all five MMTV-induced tumors, one chemical carcinogen-induced tumor, and the human tumor cell line induced transformation with high efficiencies (approx 0.2 transformant per ug of DNA). NIH cells transformed by DNAs of MMTV-induced tumors did not contain exogenous MMTV DNA sequences, indicating that MMTV-induced mammary carcinomas contained activated cellular transforming genes that were not linked to viral DNA. The transforming activities of DNAs of all five MMTV-induced tumors, the chemical carcinogen-induced mouse tumor, and the human tumor cell line were inactivated by digestion with the restriction endonucleases Pvu II and Sac I, but not by BamHI, EcoRi, HindIII, Kpn I, or Xho I. These results indicate that the same or closely related transforming genes were activated in six different mouse mammary carcinomas, induced by either MMTV or a chemical carcinogen, and in a human mammary carcinoma cell line. (Author abstract) (25 Refs)

2. GENERATION OF TRANSFORMING VIRUSES IN CULTURES OF CHICKEN FIBROBLASTS INFECTED WITH AN AVIAN LEUKOSIS VIRUS.

Stavnezer E, Gerhard DS, Binari RC, Balazs I
Genetics and Molecular Biology Unit, Graduate Sch., Sloan-Kettering Inst. for Cancer Res., New York, NY, 10021
J Virol; 39(3):920-934 1981

During serial passages of an avian leukosis virus (the transformation-defective, src deletion mutant of Bratislava 77 avian sarcoma virus, designated tdB77) in chicken embryo fibroblasts, viruses which transformed chicken embryo fibroblasts in vitro emerged. Chicken embryo fibroblasts infected with these viruses (SK770 and SK780) had a distinctive morphology, formed foci in monolayer cultures, and grew independent of anchorage in semisolid agar. Bone marrow cells were not transformed by these viruses. Another virus (SK790) with similar properties emerged during serial subcultures of chicken embryo fibroblasts after a single infection with tdB77. The 50S to 70S RNAs isolated from these viruses contained a tdB77-sized genome (7.6 kilobases), 8.7-and 5.7-kilobase RNAs, and either a 4.1-kilobase RNA or a 4.6-kilobase RNA. These RNAs did not hybridize with cDNA's representing the src, erb, mac, and myb genes of avian acute transforming viruses. Cells transformed by any one of the SK viruses (SK770, SK780, or SK790) synthesized two novel gag-related polyproteins having mol wt of 110,000 (p110) and 125,000 (p125). We investigated the compositions of these proteins with monospecific antiviral protein sera. We found that p110 was a gag-pol fusion protein which contained antigenic determinants of p19, p27, and reverse transcriptase and that p125 contained only gag determinants, leaving 49,000 daltons which was antigenically unrelated to the structural and replicative proteins of avian leukosis viruses. An analysis of the SK viral RNAs with specific DNA probes indicated that the 5.7-kilobase RNA contained gag sequences but lacked pol sequences and, therefore, probably encoded p125. The transforming ability, the deleted genome, and the induced polyproteins of the SK viruses were reminiscent of the properties of several replication-defective acute transforming viruses. (Author abstract) (51 Refs)

3. SRC GENES OF TEN ROUS SARCOMA VIRUS STRAINS, INCLUDING TWO REPORTEDLY TRANSDUCED FROM THE CELL, ARE COMPLETELY ALLELIC; PUTATIVE MARKERS OF TRANSDUCTION ARE NOT DETECTED.

Lee WH, Nunn M, Duesberg PH
Dept. Molecular Biology, Univ. California, Berkeley, CA, 94720
J Virol; 39(3):758-776 1981

We have compared the src-specific sequences of eight RSV strains and of two rRSV's to each other and to a molecular clone of the src-related chicken locus. Our comparisons are based on RNase T1-resistant oligonucleotides of RNA hybridized to src-specific cDNA, which was prepared by hybridizing RSV cDNA with RNA of isogenic src deletion mutants, or to a cloned cellular src-related DNA. All of the approx 20 src-oligonucleotides of a given RSV strain were recovered by src-specific cDNA's of all other RSV strains or by cellular src-related DNA. The number of oligonucleotides varied slightly with the length of the src deletion used to prepare src-specific cDNA, thus providing a measure for src deletion mutants. Our data indicate that the src genes are about 98% conserved and completely allelic with only scattered single nucleotide differences in certain variable regions which are subject to point mutations. We cannot distinguish between a cellular and viral origin of rRSV's. However, the following are not compatible with a cellular origin of rRSV's. (i) The only putative oligonucleotide marker which is exclusively shared by the two rRSV's studied and which differs from a parental counterpart in a single base was not detectable in cellular src-related DNA. (ii) The number of different allelic src markers observed by us and others in rRSV's was too large to derive from one or two known cellular src-related loci. (iii) The known absence of linkage of the cellular src-related locus with other virion sequences was extended to all non-src oligonucleotides, including some mapping directly adjacent to src. This is difficult to reconcile with the claim that transformation-defective, partial src deletion mutants of RSV which contain both, one, or possibly no src termini nevertheless transduce at the same frequencies, even though homologous, single or double illegitimate recombinations would be involved. Given (i) our evidence that src genes are subject to point mutation under selective conditions similar to those prevailing when rRSV's were generated and (ii) the lack of absolute evidence for the clonal purity of the transformation-defective, partial src deletion mutants of RSV used to generate rRSV's, we submit that the src genes of rRSV's could have been generated by cross-reactivation of nonoverlapping src deletions or mutation of src variants possibly present in transformation-defective, partial src deletion mutants of RSV. (52 Refs)

4. CHARACTERIZATION OF TRANSFORMATION- AND REPLICATION-SPECIFIC SEQUENCES OF RETICULOENDOTHELIOSIS VIRUS.

Cohen RS, Wong TC, Lai MM
(c/o Lai) Dept. Microbiology, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Virology; 113(2):672-685 1981

Using a combination of hybridization and oligonucleotide fingerprinting techniques we have determined the sequence relatedness of oncogenic avian reticuloendotheliosis virus (REV) to its associated helper virus, REV-A, and to the other members of the reticuloendotheliosis (RE) virus group. Our studies have shown that approx 30% of the genomic sequences of REV are unrelated to the nononcogenic RE viruses. These REV-specific, and presumably oncogenic, sequences are arranged in a contiguous fashion, possibly interrupted by a short stretch of REV-A-related sequences, localized between 1 and 2.7 kilobases (kb) from the 3'-end on the REV genome. We have also identified two regions of REV-A sequences which are deleted in the REV genome. The first region encompasses 3 kb of sequences in the 5'-half of the genome, presumably corresponding to the gag-pol genes. The second region represents 1.5(kb) of the env sequences. These deletions could account for the genetic defectiveness of REV. By studying the sequence relatedness between REV-A and the other RE viruses, we have shown that REV is the only RE virus which contains these oncogenic sequences. We have also determined the relatedness between these viruses. In addition, we have identified a hypervariable region which maps in or near the env gene. The possible significance of this region in accounting for both the varied pathogenicity of the RE viruses and the origin of oncogenic REV is discussed. (Author abstract) (39 Refs)

5. CHARACTERIZATION OF A GENE ENCODING A 115 K SUPER T ANTIGEN EXPRESSED BY A SV40-TRANSFORMED RAT CELL LINE.

May E, Jeltsch JM, Gannon F
Institut de Recherches Scientifiques sur le Cancer, B.P. no 8, 94800 Villejuif, France
Nucleic Acids Res; 9(16):4111-4128 1981

It has been reported that SV40-transformed V 11 F 1 clone 1 subclone 7 rat cells (subclone 7) produce a super T antigen of 115,000 M. This super T antigen is entirely SV40 coded and is synthesized by translation of an elongated form of SV40 early mRNA. The results reported here show that there is only one independent insertion of viral DNA in the cellular genome of subclone 7 cells. When DNA from subclone 7 cells was cleaved with Bam HI endonuclease two distinct SV40 sequence containing fragments were generated with sizes of 5 Kb and 10 Kb, respectively. Two recombinant cosmids were constructed by insertion of the 5 Kb and 10 Kb fragments, respectively, into cosmid pHC 79. Using restriction map analysis and nucleotide sequencing, we showed that the 5 Kb fragment actually contained the complete sequence of a gene encoding super T antigen. As compared to the normal SV40 early gene, the sequence of super T gene showed the following rearrangements: (i) The segment between nucleotides 4116-3544 was duplicated in a direct order and (ii) these two copies of 573 nucleotide sequence were separated by a 93 nucleotide tract which was a nearly perfect inverted repeat of the segment located between nucleotides 4868 and 4776 (nucleotide numbering used here = Weissmann number + 17). (Author abstract) (30 Refs)

6. LACK OF AKR ECOTROPIC PROVIRUS AMPLIFICATION IN AKR LEUKEMIC THYMUSES.

Yoshimura FK, Breda M
Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
J Virol; 39(3):808-815 1981

A DNA fragment from the 3' region of a molecularly cloned AKR ecotropic provirus was identified to be specific for the AKR ecotropic murine leukemia virus (MuLV). This selected DNA fragment was used to analyze the integrated MuLV proviruses in normal and leukemic tissue DNAs of AKR mice. In comparison with a DNA fragment from the 5' region of the cloned AKR genome or one representing the entire genome, this selected probe hybridized to only a few MuLV proviruses. By comparing transformed and nontransformed tissue DNAs, it appeared that no amplification of proviral sequences related to the AKR ecotropic MuLV had occurred in thymomas of AKR mice during the development of leukemia in these animals. Analysis of the AKR ecotropic MuLV proviruses revealed a significant degree of polymorphism for these sequences among individuals in the AKR/J strain of mouse. (Author abstract) (24 Refs)

TRANSFORMATION GENE EXPRESSION AND REGULATION

7. DIFFERENCE IN GENETIC EXPRESSION BETWEEN NORMAL AND TRANSFORMED WI-38 CELLS.

Nose K, Okamoto H, Namba M
Dept. Biochemistry, Toyama Medical and Pharmaceutical Univ. Sch. Medicine, Sugitani, Toyama, Japan
Cell Struct Funct; 6(2):93-101 1981

In order to study transformation-specific gene expression, total poly(A)+RNA was extracted from normal WI-38 and Co60-irradiation-transformed WI-38 (CT-1) human diploid fibroblasts, complementary DNA (cDNA) against this RNA was prepared, and hybridization studies of these two nucleic acids were performed; also, radiolabeled proteins from the normal and transformed cells were prepared and examined by two-dimensional gel electrophoresis. Poly(A)+RNA sedimenting from 5S to 23S was hybridized to cDNA fractions greater than 150 bases (av size: 300 bases) in two combinations: homologous (both nucleic acids came from the same cell type) and heterologous (the RNA and DNA came from opposite cell types); considerable hybridization occurred in both cases, showing that there is extensive homology between the poly(A)+RNAs of normal and transformed cells. Approx 200 protein spots were examined electrophoretically from both cell types, first by isoelectrofocusing and then by sodium dodecyl sulfate-polyacrylamide gel analysis followed by autoradiography: two proteins were found in the normal cells that were not present in the transformed cells, and two proteins were found in the transformed cells that were not found in the normal cells. These results indicate that transformation of human fibroblasts is accompanied by only limited alteration in genetic expression. (25 Refs)

8. TUMOR-SPECIFIC POLYADENYLATED RNA'S FROM 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED MAMMARY TUMORS REVEALED THROUGH HYBRIDIZATION WITH FRACTIONATED SINGLE-COPY DNA.

Supowit SC, Rosen JM
Dept. Cell Biology, Baylor Coll. Medicine, Texas Medical Center, Houston, TX, 77030
Cancer Res; 41(10):3827-3834 1981

Polyadenylated (poly(A)+) and nonpolyadenylated (poly(A)-) RNA fractions from primary, hormone-dependent, 7,12-dimethylbenz(a)anthracene-induced mammary tumors and normal rat mammary tissue were analyzed by molecular hybridization to determine if there is a unique class of 'tissue-specific' RNA sequences. Single-copy [3H]DNA was fractionated into probes which were either depleted of midpregnant RNA sequences or complementary to these same sequences. When these probes were annealed to homologous and heterologous poly(A)+ RNA's, distinct sets of single-copy sequences were found in the two poly(A)+ RNA populations. The complexity of the 'tumor-specific' sequences was about 6.7 x 10(7) nucleotides (assuming asymmetrical transcription). Hybridization of the poly(A)- RNA fractions isolated from the 7,12-dimethylbenz(a)anthracene-induced tumors and the normal mammary gland to poly(A)- complementary DNA's revealed that both tissues appear to contain a class of poly(A)- RNA sequences which were distinct from the set of poly(A)+ RNA's. Both poly(A)- RNA fractions saturated at 3% when hybridized to single-copy [3H]DNA. However, approx 15 to 25% (minimum estimate) of the complexity of the poly(A)- RNA was contributed by contaminating poly(A)+ RNA sequences. Therefore, the actual complexity of the poly(A)- RNA fractions was 2.0 to 2.5% of the single-copy hybrid genome. Mixtures of these two RNA fractions also gave a saturation value of 3.0% when annealed to single-copy [3H]DNA. This indicated that most of the poly(A)- RNA's were similar in the neoplastic and normal mammary tissues. Although the majority of the infrequent RNA species are held in common between the two tissues, there is a distinct set of high-complexity poly(A)+ RNA sequences, presumably of nuclear origin, which is unique to the 7,12-dimethylbenz(a)anthracene-induced tumors. Whether these RNA's are processed and became functional messenger RNA's is not known. Presumably, they play a role in regulating the frequencies of the tissue-specific abundant and moderately abundant messenger RNA's and therefore provide one mechanism by which the concentration of specific proteins and ultimately the expression of the transformed phenotype may be regulated. (Author abstract) (40 Refs)

9. DEMONSTRATION OF AVIAN SARCOMA VIRUS-CODED PP60SRC IN VIVO AND THE ANTI-PP60SRC IMMUNE RESPONSE IN CHICKENS.

Ellwart-Tschurtz M, Kurth R
Friedrich Meischer-Laboratorium, Max Planck-Gesellschaft, 7400 Tubingen, W. Germany
J Virol; 39(3):950-953 1981

The avian sarcoma virus (ASV)-coded transforming protein pp60src was originally detected in vitro in ASV-transformed avian and mammalian cells in experiments involving mammalian antisera to ASV-induced tumors. It is demonstrated here that pp60src is also expressed in vivo in ASV tumors of chickens. Furthermore, the existence of the endogenous pp60src in all chicken cells does not impair the immune response to exogenous pp60src in the chicken. Whereas chicken antibodies can bind to pp60src, they do not serve as substrates for the protein kinase activity of this transforming protein. (Author abstract) (8 Refs)

10. FOUR ROUS SARCOMA VIRUS MUTANTS WHICH AFFECT TRANSFORMED CELL MORPHOLOGY EXHIBIT ALTERED SRC GENE PRODUCTS.

Fujita DJ, Bechberger J, Nedic I
Cancer Res. Lab., Dept. Biochemistry, Univ. Western Ontario, London, Ontario N6A 5B7, Canada
Virology; 114(1):256-260 1981

Four Rous sarcoma virus Schmidt Ruppin A (RSV SR-A) morphf mutants (ST529, WO101, WO201, and WO401), independently isolated in the presence of different mutagens, cause an elongated, or fusiform, transformed cell morphology in chicken embryo fibroblasts at 37 C. The src gene products isolated from cells transformed by these mutants exhibited an apparent mol wt (Mr) of approx 54,000 to 55,000 on SDS-polyacrylamide gels, in contrast to the approx 59,000 to 60,000 Mr pp60src species isolated from wt SR-A-transformed cells, using the same extraction conditions. This difference was observed both in extraction buffers containing SDS, sodium deoxycholate, and NP-40, as well as in buffers not containing SDS and sodium deoxycholate. Partial protease digestion experiments indicated that src gene products of all four mutants were lacking peptides present in the N-terminal half of wt pp60src. The mutant src species isolated from cells transformed at 37 C exhibited kinase activity; in the case of the temperature-sensitive mutant ST529, this activity displayed a pronounced in vitro temperature sensitivity. These results strongly suggest that a common, or similar, structural alteration in 'pp60src' species of the mutants is intimately related to, and perhaps the cause of, the morphf phenotype exhibited by the cells they transform. (Author abstract) (25 Refs)

11. EXPRESSION OF VIRAL DNA IN ADENOVIRUS TYPE 12-TRANSFORMED CELLS, IN TUMOR CELLS, AND IN REVERTANTS.

Schirm S, Doerfler W
Inst. Genetics, Univ. Cologne, Cologne, W. Germany
J Virol; 39(3):694-702 1981

The expression as cytoplasmic RNA of integrated human adenovirus Type 12 (Ad12) DNA in transformed and tumor cell lines and in revertants was investigated. The transformed and tumor cells contained multiple copies of the viral genome, 3 to 22 copies per cell in different cell lines. The integrated Ad12 DNA molecules persisted intact or nearly intact and in most cases colinear with the virion DNA. In the revertant cell lines, which were derived from cell line T637 (22 copies of Ad12 DNA per cell), all of the Ad12 DNA molecules were lost (line F10) or only one copy and a fraction of a second copy persisted (line TR12). The size classes map locations of Ad12-specific cytoplasmic RNAs in three Ad12-transformed hamster cell lines (T637, HA12/7, and A2497-3), in two revertant lines (F10 and TR12), in one Ad12-induced hamster (CLAC3), and in one rat brain tumor line (RBT12/3) were determined. Cytoplasmic RNA from uninfected B3 hamster cells and from human KB cells productively infected with Ad12 served as controls. In the later control experiments, the RNA was isolated early or late postinfection. The expression of the integrated viral genomes in these lines was regulated by mechanisms more complicated than simple gene dosage effects. Using cloned fragments of Ad12 DNA as hybridization probes, we analyzed the cytoplasmic RNAs from the cell lines mentioned by electrophoresis on agarose gels, blotting, and DNA-RNA hybridization. For each transformed and tumor cell line, except for the revertants, several size classes of Ad12-specific cytoplasmic RNA were detected for the early E1, E2, and E4 regions of Ad12 DNA. Only cell lines A2497-3, T637, and RBT12/3 contained several size classes of cytoplasmic RNA homologous to the E3 region of Ad12 DNA. In preliminary experiments, we failed to detect the expression as cytoplasmic RNA of the so-called virus-associated RNA in transformed and tumor cell lines. Virus-associated RNA represents a population of low-mol-wt RNAs that map at around 30 fractional length units on the viral genome. (32 Refs)

EXPERIMENTAL MODULATION OF ONCOGENIC TRANSFORMATION

12. RETINOID-INDUCED GROWTH INHIBITION OF HERPESVIRUS-TRANSFORMED MARMOSET LYMPHOBLASTOID CELL LINES.

Abb J, Deinhardt F
Max von Pettenkofer-Institut, Pettenkoferstrasse 9a, D-8000 Munchen 2, W. Germany
Oncology; 38(6):346-350 1981

The in vitro proliferation of herpesvirus-transformed marmoset lymphoblastoid cell lines (LCL) was inhibited by retinoic acid and retinyl acetate. Both Herpesvirus-ateles- and Herpesvirus-saimiri-transformed LCL with T-cell characteristics and Epstein-Barr-transformed LCL with B-cell markers were more sensitive to retinoic acid than to retinyl acetate. Inhibition of LCL proliferation was dependent on retinoid concentration and became apparent only after 3-4 days of exposure. In vitro assays for marmoset LCL sensitivity to retinoids may indicate the potential usefulness of these compounds in the chemoprevention of virus-induced lymphoma in vivo. (Author abstract) (28 Refs)

13. INCREASED PHOSPHOTYROSINE CONTENT AND INHIBITION OF PROLIFERATION IN EGF-TREATED A431 CELLS.

Gill GN, Lazar CS
Dept. Medicine, Div. Endocrinology, Univ. California San Diego, Sch. Medicine, La Jolla, CA, 92093
Nature; 293(5830):305-307 1981

The effect of epidermal growth factor (EGF) on phosphotyrosine content of exponentially growing A431 human epidermoid carcinoma cells was determined by labelling cells to equilibrium with 32P-orthophosphate, treating replicate plates 3 hr with EGF, and measuring phosphotyrosine. EGF increased phosphotyrosine content 7x from 0.02 to 0.14% of cellular phosphoamino acids, indicating that EGF activates tyrosine-specific protein kinase activity in vivo as it does in vitro and the kinase activity is an important component of the mechanism of EGF action. In contrast to Rous sarcoma virus (RSV) transformation, EGF inhibits replication of A431 cells. No growth was apparent when A431 cells were maintained with saturating concentrations of EGF over a 14-day period. Affinity of EGF receptors for EGF was inversely related to cell density. The measured equilibrium dissociation constant, Kd, for EGF binding at low and high cell densities was higher than the half-maximally effective concentration, EC50, of EGF required to inhibit cell proliferation at that cell density (7x at 500 cells/square cm and 4x at 15,000 cells/square cm). Occupancy of only a fraction of EGF receptors seems to be required for growth inhibition. Dose-response of growth inhibition was strongly affected by tissue culture substratum. (36 Refs)

14. TRANSFORMATION-ENHANCING ACTIVITY OF GELATIN-BINDING FRAGMENTS OF FIBRONECTIN.

De Petro G, Barlati S, Vartio T, Vaheri A
Dept. Virology, Univ. Helsinki, 00290 Helsinki 29, Finland
Proc Natl Acad Sci USA; 78(8):4965-4969 1981

Studies have established that cryoprecipitates of the plasma of tumor patients contain a biological activity enhancing morphological cell transformation (transformation-enhancing factor; TEF) in cultures of chicken embryo fibroblasts infected with temperature-sensitive mutants of Rous sarcoma virus. We report here that similar TEF activity is effected by defined fragments of human plasma fibronectin obtained by limited digestion with major humoral or tissue proteinases. TEF activity was obtained from plasminolytic fragments of fibronectin and from cathepsin G-treated fibronectin. No activity was recorded from intact dimeric fibronectin or its reduced and alkylated subunits, from fibrinogen or its plasminolytic fragments, or from plasmin (EC 3.4.21.7) or cathepsin G (EC 3.4.21.20) treated or untreated with proteinase inhibitors. All of the TEF activity of the proteolytic fragments of fibronectin was located on the gelatin-binding peptides. The minimum effective doses in the TEF assay were 750 ng/ml of plasmin-treated fibronectin, 100 ng/ml of gelatin-binding plasminolytic fibronectin (enriched in Mr 180,000-190,000 polypeptides), and 100 ng/ml of gelatin-binding fragments of cathepsin G-treated fibronectin (enriched in a Mr 30,000 fragment). TEF activity of proteinase-treated fibronectin was inhibited by gelatin and by intact dimeric fibronectin. The potent TEF activity of proteolytic fragments of fibronectin raises the possibility that they may have a role in malignant transformation. (Author abstract) (32 Refs)

15. DIFFERENTIATION OF THE MECHANISMS OF ONCOGENICITY OF 1,4-DIOXANE AND 1,3-HEXACHLOROBUTADIENE IN THE RAT.

Stott WT, Quast JF, Watanabe PG
Toxicology Res. Lab., Dow Chemical U.S.A., Midland, MI, 48640
Toxicol Appl Pharmacol; 60(2):287-300 1981

Two tumorigenic agents, 1,4-dioxane (DX) and 1,3-hexachlorobutadiene (HCBD) were compared to the known mutagen dimethylnitrosamine (DMN) to determine whether their actions were by a genetic or nongenetic mechanism. Male Sprague Dawley rats were given tumorigenic doses of DX in drinking water (0, 10 or 100 mg/kg/day for 11 wk), HCBD by gavage (0, 0.2, or 20 mg/kg/day for 3 wk), or DMN by gavage (3 mg/kg/day for 3 wk). Other groups of rats were given single doses of DX (10, 100, 1,000 mg/kg), HCBD (0.2, 20 mg/kg), or DMN (3 mg/kg) by gavage. DX produced no genotoxic effects at tumorigenic doses. A single large dose produced no alkylation of DNA or increase in DNA repair. Repeated high doses of DX were hepatotoxic. HCBD produced a minor genotoxic effect compared with DMN. DNA repair in renal tissue was increased 1.27-1.54-fold by HCBD (20 mg/kg); DNA alkylations occurred at the rate of 0.78 per 10(6) nucleotides. No mutations were produced in the Ames' bacterial mutagenesis assay. HCBD produced renal cytotoxicity. Apparently DX induces tumors by a nongenetic mechanism. HCBD acts primarily in a nongenetic way, but is weakly genotoxic. Risk from either compound is likely only at cytotoxic doses. (34 Refs)

16. ONCOGENIC TRANSFORMATION AND CELL LYSIS IN C3H/10T1/2 CELLS AND INCREASED SISTER CHROMATID EXCHANGE IN HUMAN LYMPHOCYTES BY NICKEL SUBSULFIDE.

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Inst. Pathology, Univ. Oslo, Rikshosptalet, National Hosp., Oslo, Norway
Cancer Res; 41(10):4136-4139 1981

We have scored frequency of transformation and appearance of the oncogenic marker 'long microvilli' in mouse embryo fibroblast C3H/10T1/2 cells in culture for the compound Ni3S2. Furthermore, we have scored for Ni3S2-induced sister chromatid exchange in cultured human lymphocytes. Nickel subsulfide in moderate doses caused morphological transformation to

Type I, II, and III foci and induced long microvilli on the cells in the transformed cultures, demonstrating oncogenic transforming ability. Higher doses led to cell lysis after a lag period. The carcinogenic potency of Ni3S2 in this system was not as strong as that of methylcholanthrene. Ni3S2 increased the sister chromatid exchange frequency in human lymphocytes in a marginal, not dose-dependent way. The increased sister chromatid exchange may indicate that the carcinogenic effect of Ni3S2 is genetic rather than epigenetic. (Author abstract) (39 Refs)

17. INHIBITION OF ADENOVIRUS-TRANSFORMED CELL ONCOGENICITY BY ADENO-ASSOCIATED VIRUS.

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Virology; 113(2):521-533 1981

Adeno-associated virus (AAV) has been shown to inhibit the oncogenicity and transforming ability of adenovirus (Ad). Using the H14b Ad-transformed hamster cell line, we have developed a model system in which to characterize the molecular events responsible for these inhibitory effects. AAV infection of H14b cells decreases their oncogenicity by approx threefold. The tumors that do arise are significantly smaller and have a longer latent period. AAV infection also alters the in vitro properties of the H14b cells, reducing cloning efficiency in methyl cellulose by 38-92% and saturation density by two- to four-fold. The molecular basis of this inhibition appears to be an inhibition of production of the 58K tumor antigen as determined by fluorescent antibody and immunoprecipitation studies. The reduction in the levels of tumor antigens are not due to alterations or loss of the Ad genome within H14b cells but may reflect an alteration in transcription or processing of Ad-specific mRNA. AAV infection of H14b cells does not lead to detectable levels of AAV DNA synthesis, but some AAV transcripts are made. This is the first instance in which AAV transcription has been detected in an Ad-transformed cell line. (Author abstract) (42 Refs)

18. COCARCINOGENIC EFFECT OF VACCINIA VIRUS AND HERPES SIMPLEX VIRUS IN TISSUE CULTURE.

Mazurenko NP, Merekalova ZI, Pavlish OA, Bykovskii AF, Kurtsman MIa, Mazurenko NN

All-Union Cancer Res. Center, Moscow, USSR

Vestn Akad Med Nauk SSSR; (7):3-10 1981

Cocarcinogenic effect of vaccinia virus (VV) and herpes simplex virus (HSV) was studied in transplantable murine cell lines. The cultured cells of embryonal tissue of BALB/c mice were infected with VV, and the expression of structural protein p30 was assayed by indirect immunofluorescence reaction. Specific cytoplasmatic fluorescence was recorded in 15-20% of cells. Max fluorescence was observed 48-72 hr after infection, which corresponded to the onset of Rauscher leukemia virus replication. HSV-2 caused malignant transformation of BALB/3T3 cells. Inoculation of irradiated BALC/c mice with transformed cells (subclones 333-0 and 333-1) produced tumors in 25% and 80% of the animals. Transformed cells expressed the endogenous murine retrovirus Type 3. (29 Refs) (In RUS)

BIOCHEMICAL AND MOLECULAR BIOLOGICAL STUDIES OF TRANSFORMED PHENOTYPE

19. PHOSPHORYLATION OF THE ABELSON MURINE LEUKEMIA VIRUS TRANSFORMING PROTEIN.

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Dept. Microbiology, Molecular Biology Inst., Univ. California, Los Angeles, CA, 90024

J Virol; 39(3):870-878 1981

The Abelson murine leukemia virus transforming gene product is a phosphorylated protein encoded by both viral and cellular sequences. This gene product has an amino-terminal region derived from the gag gene of its parent virus, and a carboxyl-terminal region (abl) derived from a normal murine cellular gene. Using a combination of partial proteolytic cleavage techniques and antisera specific for gag and abl sequences, we mapped in vivo phosphorylation sites to different regions of the protein. Phosphoproteins encoded by strain variants and transformation-defective mutants of Abelson murine leukemia virus with defined deletions in the primary sequence of abl region were compared by two-dimensional limit digest peptide mapping. Specific phosphorylation pattern differences for wild-type and mutant proteins probably represented deletions of specific phosphate acceptor sites in the abl region. An in vitro autophosphorylation activity copurified with the Abelson murine leukemia virus protein from transformation-competent strains. A peptide analysis of such in vitro reactions demonstrated that these phosphorylation sites were restricted to the amino-terminal region, and the specific sites appeared to be unrelated to the sites found on proteins phosphorylated in vivo. Thus, the autophosphorylation reaction probably correlates with an activity important in transformation, but the specific end product in vitro bears little resemblance to its function in vivo. (Author abstract) (34 Refs)

20. ANALYSIS OF THE NONVIRAL ANTIGENS IMMUNOPRECIPITABLE BY SV40 T ANTIBODY FROM SV40-TRANSFORMED HUMAN/MOUSE HYBRID CELL LINES.

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Virology; 114(1):149-160 1981

The expression of nonviral antigens, ie, host-coded proteins with mol wt from 48,000-56,000 (48K-56K) immunoprecipitable from extracts of simian virus 40 (SV40)-infected or -transformed cells by anti-SV40 tumor antibody, was examined in four SV40-transformed human cell lines, one SV40-transformed mouse cell line, and eight SV40-transformed human/mouse somatic cell hybrid cell lines produced by fusion of SV40-transformed human cells with untransformed mouse cells. Differences were found in the patterns of expression of these viral induced proteins among the human cell lines, between the human and the mouse cell lines, and between the human/mouse somatic cell hybrid cell lines and the human lines from which they were derived. Two of the human cell lines expressed only a 55K nonviral antigen; two expressed both a 55K and a 52K nonviral antigen. The mouse cell line expressed both a 55K and a 48K nonviral antigen. Each hybrid cell line expressed a 55K and also a 48K nonviral antigen, except one. The BALB IV-8 hybrid cell line expressed 55K and 52K nonviral antigens. By comparing the tryptic peptides fractionated on cation exchange columns of the nonviral antigens we determined: (1) the 48K nonviral antigen in human/mouse hybrids is encoded by a mouse chromosome. (2) The 52K nonviral antigen in the BALB IV-8 human/mouse hybrid is encoded by a mouse chromosome. It is possibly a precursor to the mouse 48K protein because it contains one extra tryptic peptide in addition to those of the mouse 48K protein, because one peptide has an altered mobility and because the 52K protein is found, so far, only in a human/mouse hybrid that does not exhibit a 48K nonviral antigen. (3) The 55K nonviral antigen in the C57-VII-6 human/mouse hybrid is encoded by a human chromosome. In the BALB IV-8 human/mouse hybrid, there is a 55K protein encoded by a human chromosome and probably a 55K protein encoded by a mouse chromosome. (4) If the gene encoding the human 55K nonviral antigen is located on a single chromosome, it is located on human chromosome 7. (Author abstract) (25 Refs)

21. TWO CELLULAR PROTEINS THAT IMMUNOPRECIPITATE WITH THE TRANSFORMING PROTEIN OF ROUS SARCOMA VIRUS.

Oppermann H, Levinson AD, Levintow L, Varmus HE, Bishop JM, Kawai S
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Virology; 113(2):736-751 1981

The transforming gene (src) of Rous sarcoma virus encodes a 60,000-dalton phosphoprotein (pp60src) with the ability to phosphorylate tyrosine in certain protein substrates. The enzymatic activity of pp60src is thought to mediate neoplastic transformation by src. It would therefore be useful to identify cellular proteins that interact with pp60src on the chance that these proteins might be substrates for the kinase activity of the viral protein or be otherwise involved in neoplastic transformation of the host cell. In pursuit of this objective, we characterized the proteins that coprecipitate with pp60src in immune complexes. These proteins proved to be of two types. (i) Most immune complexes contained a series of proteins (50,000 to 58,000 daltons) that were apparently derived from pp60src by sequential degradation from the amino terminus. (ii) Two proteins (50,000 and 89,000 daltons) coprecipitated with pp60src, probably by virtue of their ability to bind to the viral protein. We used temperature-sensitive mutants in src to explore the possibility that the two cellular proteins might be substrates for the protein kinase activity of pp60src: propagation of infected cells at the nonpermissive temperature failed to affect the phosphorylation of either of the proteins. We conclude that at least two cellular proteins are associated with pp60src prior to immunoprecipitation with antisera directed against the viral protein. It is possible that neither of these proteins is a substrate for the protein kinase activity of pp60src, however, and their role in neoplastic transformation by src (if any) remains moot. (38 Refs)

22. TRANSFORMATION-DEPENDENT QUANTITATIVE CHANGES IN GLYCOPEPTIDE BINDING TO CONCANAVALIN A-SEPHAROSE.

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Cancer Lett; 14(1):55-62 1981

Quantitative changes in concanavalin A (Con A)-Sepharose binding of differentially L-fucose-labeled glycopeptides from a newly established Syrian golden hamster (SGH) fetal lung cell line as a control, and transformed and tumor cell lines derived from the SGH line, were investigated. Cochromatography on Sephadex G50 was used to detect transformation-dependent mol wt changes in the glycopeptides of the new cell lines. M3E3/C3 is the established cell line from SGH fetal lung. SA 17, SA Ru, and SA F1 were chemically transformed clones, SA17T, SAF1T, and SA RuT were established by recultivation of dissected solid tumors induced in allogeneic hosts after injection of transformed lines. Con A-Sepharose chromatography demonstrated that for SA 17T and M3E3/C3 lines, surface glycopeptides were composed of predominantly non-binding meterial, while the main part of control glycopeptides was bound to the column. In the tumor lines, the part of non-binding glycopeptides was further augmented and the binding part was concomitantly decreased compared to the transformed parent line. In all transformed and tumor cell lines investigated, the quantitative change in Con A binding was paralleled by a shift of transformed or tumor glycopeptides to higher apparent mol wt compared to the control in gel chromatography. (24 Refs)

23. ETHER LIPID STUDIES IN MOUSE C3H/10T1/2 CELLS AND A 3-METHYLCHOLANTHRENE-TRANSFORMED CLONE.

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Medical and Health Sciences Div., Oak Ridge Associated Univ., Oak Ridge, TN, 37830
Arch Biochem Biophys; 211(1):240-244 1981

Future application of the C3H/10T1/2 mouse embryo cell culture model to studies of ether-linked lipids in cancer cells was examined. Two C3H/10T1/2 cell lines were tested: clone 8, a nontumorigenic, nontransformed line maintaining normal morphology through passages 15-20, and clone 16, a highly tumorigenic line derived from clone 8 by transformation with 3-methylcholanthrene. Synthesis of complex glycerolipids was measured using [1-14C]-hexadecanol. After 3 hr incubation, clone 8 cells contained 26% of radioactivity in free intracellular alcohol, 52% in phospholipids, and 22% in neutral glycerolipids. Bonding in lipids included 55% ester and 18.6% ether bonds. Incubation with [1-3H]-hexadecanol revealed the higher percentage of alkyldiacylglycerol-associated radioactivity present in clone 16 cells (9.0%) than in clone 8 cells (4.8%). Clone 16 cells contained more labeled phosphatidylcholine (PC) than phosphatidylethanolamine (PE), whereas clone 8 cells contained more PE than PC. Clone 16 cells showed a decreased ability to oxidize fatty alcohols and incorporate the resulting carboxylic acid into acyl groups. Results demonstrate that elevated ether-linked lipids characteristic of neoplastic cells are also found in a transformed tumorigenic clone of C3H10T1/2 cells in vitro. Increased levels of ether-linked lipids in transformed cells may be partially regulated by the availability of fatty alcohol precursors. (23 Refs)

24. TEMPERATURE-DEPENDENT AND TRANSFORMATION-ASSOCIATED CHANGES IN POLYAMINE METABOLISM IN NORMAL AND ROUS SARCOMA VIRUS-INFECTED CHICK EMBRYO FIBROBLASTS.

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Biochim Biophys Acta; 677(1):1-6 1981

Tertiary cultures of chick embryo fibroblasts infected and transformed by the wild-type Rous sarcoma virus, when actively growing at 35 C, had higher putrescine levels than the respective uninfected cells. Transformed cells also had much higher specific activity of ornithine decarboxylase (EC 4.1.1.17) than the normal fibroblasts. At 41 C the difference in putrescine levels between the normal and the transformed cells was less marked, and both cell types showed a relative accumulation of spermine. Cultures infected with the NY68 mutant virus, which is temperature-sensitive for transformation, showed a 41 C normal cell morphology and intermediate polyamine pattern, while at 35 C a transformed phenotype was found in both aspects. In shift-down experiments a change towards the permissive temperature pattern of polyamine metabolism was evident within 2-3 hr. Difluoromethylornithine, a specific and irreversible inhibitor of ornithine decarboxylase efficiently reduced the enzyme activity as well as the levels of both putrescine and spermidine in all culture types and temperatures. Incubation of Rous sarcoma virus-transformed cells with 3 mM difluoromethylornithine for 36 hr did not affect the maintenance of the transformed state. Likewise, when NY68-infected cultures were exposed to difluoromethylornithine at 41 C for 12 hr and then shifted down to 35 C, the appearance of the transformed morphology took place concomitantly with th at of the control cultures without respective changes in the polyamine levels. This suggests that the transformation-associated pattern of polyamines in chick embryo fibroblasts is not a prerequisite for morphological transformation of these cells. (Author abstract) (27 Refs)

25. BIOCHEMICAL STUDIES ON BOVINE ADENOVIRUS TYPE 3. V. SOME PROPERTIES OF MOUSE CELLS TRANSFORMED WITH VIRAL DNA FRAGMENTS.

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Cell Struct Funct; 6(2):121-131 1981

Tumorigenicity and cell-surface properties were studied in mouse A31 cells (a BALB/3T3 clone) transformed by fragments of the bovine adenovirus type 3 (BAV3): the EcoRI D fragment (3.6 to 19.7 map units; TrD1 cells) or the HindIII J-E ligated fragment (0 to 11.9 map units; TrJE6 cells). DNA-DNA reassociation kinetics experiments showed that both TrD1 and TrJE6 cells contained copies of the transforming region of BAV3. Hybridization experiments between RNA from transformed cells and BAV3 DNA showed that BAV3-specific RNA was synthesized in the transformed cells. Biochemically, both transformed cell lines showed increased uptake of 2-deoxyglucose compared with that by normal A31 cells, agglutination by plant lectins (concanavalin-A, wheat germ agglutinin, castor bean agglutinin, and Wistaria floribunda agglutinin) with different sugar specificities at lower concentrations of lectins than needed to agglutinate A31 cells, and higher activity of plasminogen activator than present in A31 cells. Both transformed cell lines produced tumors within 2 mo when inoculated into mice (10(3)-10(7) cells/mouse), whereas 10(7) A31 cells did not produce tumors. These results indicate that the altered properties of the transformed cells examined in these studies are directly or indirectly controled by the gene(s) located between map units 3.6 and 11.9 of the BAV3 genome. (32 Refs)

26. EFFECTS OF VIRAL TRANSFORMATION ON SYNTHESIS AND SECRETION OF COLLAGEN AND FIBRONECTIN-LIKE MOLECULES BY EMBRYONIC CHICK CHONDROCYTES IN CULTURE.

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J Biol Chem; 256(17):9111-9117 1981

Monolayer cultures of chondrocytes isolated from 11-day-old chick embryo vertebral cartilage were transformed by Rous sarcoma virus, and the effects of transformation on synthesis and secretion of extracellular proteins by these cells were studied. Transformation resulted in decreased synthesis of Type II collagen which did not appear to be due to underhydroxylation of collagenous protein but to a decrease in the total amount synthesized. Carboxymethyl-cellulose chromatography and polyacrylamide disc gel electrophoresis failed to demonstrate any alpha2 chains as a result of the transformation, suggesting that conversion of Type II to Type I collagen did not occur. In contrast to the decrease in collagen synthesis, synthesis of a molecule with biochemical characteristics similar to fibronectin increased markedly in virally transformed cultures. Although there were no significant differences in the amount of fibronectin-like molecules in the cell layers of normal and transformed chondrocytes, a marked increase of these molecules in the culture media of the transformed cells was demonstrated. These findings were confirmed by experiments with temperature-sensitive mutants of the virus. (Author abstract) (37 Refs)

27. X-RAY MICROANALYSIS OF ELECTROLYTE CONTENT OF NORMAL, PRENEOPLASTIC, AND NEOPLASTIC MOUSE MAMMARY TISSUE.

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Cancer Res; 41(10):3877-3880 1981

Intracellular sodium, chlorine, and potassium concentrations (mmol/kg dry wt) were determined by electron probe x-ray microanalysis of an individual epithelial cells in freeze-dried 2-um sections of mouse mammary tissue which were cut at-30 C. A model system was utilized in order to compare elemental content of cells from normal pregnant mammary tissue and preneoplastic and neoplastic mammary tissues from female BALB/cCrlMed mice. Animals were killed by cervical dislocation, and tissue was rapidly frozen in liquid propane. Normal mammary glands were obtained from primiparous mice at 16 or 17 days of gestation. Tissue from the hyperplastic alveolar nodule line D1 was removed from donor mice 12 to 16 wk after transplantation into the cleared mammary fat pad. All mammary adenocarcinomas, D1T, were primary tumors which developed in mice with transplants of nodule line D1. Data were collected from five animals (10 cells/animal) in each of the three groups. It was found that the electrolyte content of cells of preneoplastic tissue was the same as that of the normal mammary tissue but was significantly elevated in neoplastic tissue (162, 130, and 48% increases for sodium, chlorine, and potassium, respectively). Thus, an increase in electrolyte content seems to be associated with the transformation to a neoplastic state and not associated with conversion to the preneoplastic state. (Author abstract) (30 Refs)

28. RESTRICTION ENDONUCLEASE ANALYSIS OF MITOCHONDRIAL DNA FROM VIRUS-TRANSFORMED, TUMOR AND CONTROL CELLS OF HUMAN, HAMSTER AND AVIAN ORIGIN. SEQUENCE CONSERVATION AND INTRASPECIFIC VARIATION.

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Biochim Biophys Acta; 655(2):210-220 1981

This study compares over 70 recognition sites for restriction endonucleases on m tDNAs from various control versus malignant cells, derived from Syrian hamster, chick embryo, viper and human cells, exhibiting a wide spectrum of cellular transformation and tumor histories. Agents for transformation in vitro and in vivo include Rous sarcoma viruses, simian virus 40, polyoma virus and adenovirus. The results show a striking intraspecific sequence homogeneity of different mtDNAs regardless of tissue origin and oncogenic history. mtDNA from human biopsy specimens of tumor versus pathologically normal areas yielded indistinguishable restriction cleavage patterns reflecting either the 'wild-type' form (with 7 restriction endonucleases) or, in one individual, a variant pattern detected with HpaI. The precise position of the HpaI variant site was determined on the physical map of human mtDNA. Additional cleavage sites in the previously reported restriction map of Syrian hamster mtDNA are also presented. It is concluded that (1) mtDNA sequences in higher animal cells are highly conserved in malignant transformation; (2) no evidence for integration of viral sequences in mtDNA is apparent; (3) variant patterns in mtDNA are likely to be intraspecific polymorphisms that pre-exist neoplastic transformation. The possibility is discussed that altered regulatory interaction with the mitochondrial genome, rather than evident changes in mtDNA primary structure, determine anomalous mitochondrial functions in malignant transformation. (Author abstract) (62 Refs)

29. SPECTACULAR CANCER MECHANISM DOUBTED. CORNELL RETRACTS REPORTS OF KINASE CASCADE.

Stein MD
No affiliation given
Nature; 293(5828):93 1981

A Cornell University laboratory study implicated a protein kinase cascade as the mechanism by which the products of RNA tumor virus genes transform normal cells into tumor cells. Cornell and other laboratories have been unable to reproduce the results. (2 Refs)

CELL SURFACE PHENOMENA OF TRANSFORMATION

30. CELL-MATRIX INTERACTIONS IN DEVELOPMENT AND NEOPLASIA.

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Oncodev Biol Med; 2(4):295-303 1981

A review of cell-matrix interactions is presented. It is now commonly believed that cells communicate with the extracellular matrix that surrounds them and that this communication influences differentiation. Significant progress was recently made in understanding the chemistry of the extracellular and basement membrane macromolecules, including collagens, fibronectin, and laminin. Attachment of cells to component macromolecules of extracellular matrixes has been used as an indicator of a primary interaction of cells with extracellular matrix; these interactions may subsequently lead to changes in gene expression in adherent cells. Cells plated on dishes coated with fibronectin attach and spread rapidly; the actual function of fibronectin is not known, but it mediates the attachment of most types of cells, promotes cell motility, prevents fusion of myoblasts and differentiation of chondrocytes, and acts as an opsonin in plasma. Laminin also appears to promote cell attachment, but with a more restricted specificity than fibronectin. Fibronectin and other proteins mediate the attachment of cells to collagen. Fibronectin may play a role in directing differentiation and morphogenetic movements in certain cells. Laminin may be involved in tissue organization, cell proliferation, and differentiation. Transformed cells have greatly reduced amounts of fibronectin on their surfaces and reduced amounts of collagen production. Laminin in malignant cells has not yet been well studied. The possible importance of altered cell-matrix interactions in tumorigenesis are discussed. (68 Refs)

31. CELL MEMBRANE CHARACTERISTICS AND BIOLOGICAL BEHAVIOR OF VIRUS TRANSFORMED CELLS.

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Klin Wochenschr; 59(17):957-964 1981

The transformation of a normal into a tumor cell is not caused by a single molecular event, but is the consequence of several simultaneous or consecutive molecular processes, which lead to a variety of changes in the structure and the metabolism of the cell. Investigations with the Rous sarcoma virus show that a single gene is primarily responsible for these changes that is coding for a phosphoprotein which, however, is multifunctional. The biochemical and biologic events which initiate and maintain the transformed status of the cell involve mainly the cytoplasmic membrane. At both the outer and the inner surface of the cell membrane dramatic changes occur which influence the cell structure, permeability of the cytoplasmic membrane, and the intracellular metabolic pathways. Most probably, these transformation-associated events are also involved in cell proliferation under physiologic conditions. In the tumor cell, however, they are not further regulated physiologically, with the consequence of an uncontrolled and incessant cell division. (Author abstract) (30 Refs) (In GER)

MORPHOLOGICAL AND OTHER BIOLOGICAL ASPECTS OF ONCOGENIC TRANSFORMATION

32. TUBULIN ASSEMBLY SITES AND THE ORGANIZATION OF CYTOPLASMIC MICROTUBULES IN CULTURED MAMMALIAN CELLS.

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Dept. Cell Biology, Baylor Coll. Medicine, Houston, TX, 77030
J Cell Biol; 90(3):554-562 1981

The number, distribution, and nucleating capacity of microtubule-organizing centers (MTOCs) has been investigated in a variety of cultured mammalian cells. Most interphase cells contain a single MTOC that is localized at the centrosome region and corresponds to the centriole and pericent riolar material. MTOCs, like centrioles, become duplicated during the S phase of the cell cycle and are equationally distributed to daughter cells in mitosis. Multiple MTOCs were rarely observed in cultured cells except in one cell line (neuroblastoma), which also displayed an equally large number of centrioles in the cytoplasm. The kinetics of microtubule assembly and the tubulin nucleating capacity of MTOCs are assayed by incubating tubulin-depleted, permeabilized 3T3 and simian virus 40-transformed 3T3 cells with phosphocellulose-purified 6S brain tubulin and microtubule assembly buffer. Initiation and assembly of 6S tubulin occurred in association with the cells' endogenous MTOCs, and the length, number, and distribution of microtubules generated about the organizing centers were regulated and cell specific. Our results are consistent with the notion that the specification of microtubule length, number, and spatial arrangement resides largely in the MTOCs and surrounding cytoplasm and not in the tubulin subunits. (Author abstract) (34 Refs)

33. F-ACTIN AGGREGATES IN TRANSFORMED CELLS.

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J Cell Biol; 90(3):797-802 1981

Polymerized actin has been found aggregated into distinctive patches inside transformed cells in culture. The F-actin-specific fluorescent probe, nitrobenzoxadiazole-phallacidin, labels these F-actin aggregates near the ventral cell surface of cells transformed by RNA or DNA tumor viruses, or by chemical mutagens, or spontaneously. Their appearance in all eight transformed cell types studied suggests their ubiquity and involvement in transformation morphology. Actin patches developed in normal rat kidney (NRK) cells transformed by a temperature-sensitive mutant of Rous sarcoma virus (LA23-NRK) within 30 min after a shift from the nonpermissive (39 C) to the permissive temperature (32 C). Patch appearance paralleling viral src gene expression tends to implicate pp60src kinase activity in destabilizing the cytoskeleton. However, appearance of the actin aggregates in cells not transformed by retrovirus calls for alternative mechanisms, perhaps involving an endogenous kinase, for this apparently common trait. (Author abstract) (26 Refs)

34. ASSOCIATION OF PHENOTYPIC REVERSION OF TRANSFORMED CELLS INDUCED BY INTERFERON WITH MORPHOLOGICAL AND BIOCHEMICAL CHANGES IN THE CYTOSKELETON.

Brouty-Boye D, Cheng YS, Chen LB
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Cancer Res; 41(10):4174-4184 1981

The distribution of microfilament bundles, intermediate filaments, microtubules, vinculin plaques, and extracellular fibronectin matrices was examined by indirect immunofluorescence in x-ray-transformed C3H/10T1/2 cells. The transformed phenotype correlated with a lack of actin cables and vinculin-containing plaques. Both interferon-treated and untreated transformed cells displayed a similar distribution of mitochondria, intermediate filaments, microtubules, and fibronectin. Significant qualitative and quantitative differences between the two types of cells were found in the proteins associated with the cytoskeletal framework by two-dimensional gel analysis. (Author abstract) (27 Refs)

35. HUMAN CELL TRANSFORMATION BY SIMIAN VIRUS 40. BIOLOGIC FEATURES OF CLONED LINES.

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Exp Cell Res; 134(2):425-432 1981

Nine lines of doubly cloned Simian Virus 40 transformed human fibroblasts have been isolated. Precrisis in vitro characteristics of growth rate, saturation density, T antigen expression, growth in methylcellulose suspension, protease production and infectious center formation were widely divergent, although distinct for individual lines. Lines with higher T antigen expression had higher growth rates and saturation densities but grew less well in methylcellulose. Chromosome counts in most proliferating lines were in the 38-48 range; one line had 67, whereas another, poorly growing line showed 22. No distinguishing chromosomal abnormalities were present. This biologic heterogeneity suggests distinct molecular differences underlying transformation in the lines and emphasizes the importance of considering various factors as indicative of the transformed state. (Author abstract) (33 Refs)

36. CELLULAR DIFFERENTIATION AND NEOPLASIA: CHARACTERIZATION OF SUBPOPULATIONS OF CELLS THAT HAVE NEOPLASIA-RELATED GROWTH PROPERTIES IN SYRIAN HAMSTER EMBRYO CELL CULTURES.

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Proc Natl Acad Sci USA; 78(8):4995-4999 1981

Cellular subpopulations having two of the growth properties of neoplastically transformed cells - lack of postconfluence inhibition of cell division (CI-) and anchorage independence of growth (AD-) - were found in cell cultures established from 10-to 13-day-old Syrian hamster embryos. The subpopulations having these properties decrease with increasing gestation period of the embryo as well as with continuing passage in vitro. The decrease in these subpopulations was also observed when they were cultured on a lethally irradiated confluent monolayer of contact-inhibited cells (cell mat), a selection condition for CI- cells. Therefore, negative selection cannot be the explanation for the loss of CI- cells in the population, leaving two other possibilities: either the loss of proliferative capacity of the CI- cells or the acquisition of sensitivity to postconfluence inhibition of cell division (CI+) of this subpopulation on in vitro culture or in vivo growth. The CI- subpopulations were isolated clonally from cell mats and were cultured continuously on both cell mats or plastic dishes. The results indicate that these cells did not lose proliferative capacity but acquired the contact-inhibited phenotype. This result, together with the fact that embryonic development in vivo also decreases CI-/AD- subpopulations, suggests that the disappearance of these subpopulations is due to cellular differentiation of the CI-/AD- cells to become CI+/AD+ cells. (Author abstract) (24 Refs)

37. CHARACTERIZATION OF SARCOMA-POSITIVE, LEUKEMIA-NEGATIVE (S+L-) HUMAN CELLS INDUCED BY THE FELINE LEUKEMIA VIRUS PSEUDOTYPE OF MOLONEY SARCOMA VIRUS.

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Lab. Cellular and Molecular Biology, NCI, NIH, Bethesda, MD, 20205
Proc Soc Exp Biol Med; 167(4):597-606 1981

The isolation and characterization of sarcoma-positive, leukemia-negative (S+L-) human cells induced by the feline leukemia virus pseudotype of Moloney sarcoma virus (Mo-MSV(FeLV)) is reported. The four clones selected for study were negative for infectious virus and type C virus particles, but, contained a rescuable MSV genome and murine leukemia virus (MuLV)-specific antigen, such as the gag gene products, p15, p12, and p30, and lacked the env gene protein (gp 70). The cells were all tumorigenic in nude mice. In human, NRK, and NIH 3T3 mouse embryo cells, the Mo-MSV rescued by baboon type C virus (M-7), Mo-MSV(M-7), readily produced foci. Human cells transformed by MoMSV(M-7) were virus producers, while Mo-MSV(M-7)-transformed NRK and NIH 3T3 mouse embryo cells were S+L- cells. These latter cells were negative for infectious virus but contained a rescuable MSV genome and MuLV antigen. (21 Refs)

ASSAYS OF ONCOGENIC TRANSFORMATION

38. THE IMPORTANCE OF SHORT TERM EXPOSURE OF C3H 10T1/2 CELLS TO POLYCYCLIC HYDROCARBONS: EVIDENCE FOR HYDROCARBON-MEDIATED ANTICARCINOGENIC ACTIVITY.

Sarrif AM, Strobel-Stevens J, Miller C, Smythies JR
Dept. Pharmacology, Univ. Alabama in Birmingham Medical Center, Birmingham, AL, 35255
Cancer Lett; 13(4):291-297 1981

The effects of short term exposure of C3H 10T1/2 mouse embryo cells to benzo[a]pyrene (BP) and 3-methylcholanthrene (3-MC) were studied. Within the concentration range of 0.3 to 10 ug/ml, increasing the time of exposure from 15 min to 24 hr did not alter cytotoxicity (as determined by plating efficiency) appreciably; cell survival ranged between 70-90% of control. For both carcinogens, transformed foci were observed in as little as 15 min. Between 0.3-1.25 ug/ml BP, transformation frequency (TF) (the number of transformed foci/1,000 surviving cells) increased with time of exposure; at concentrations between 2.5-10 ug/ml a max TF of 2 was observed for cells exposed to BP for 3 hr. Exposure to high concentrations of 3-MC produced an optimal TF after 30 min to 1 hr. The dependency of TF on BP or 3-MC concentration at selected times was profiled. One hr exposure produced a TF which increased with increasing concentrations. After BP exposure for 3 hr, TF reached a max of 2 at 5 ug/ml; after 6 hr TF peaked at 1.25 ug/ml and decreased at higher concentrations. Results with 3-MC differed: with a 3 hr incubation TF peaked at 1.25 ug/ml and at 24 hr 0.625 ug/ml caused max TF. The changes observed in TF were not likely to result from toxic effects. In this study the transformation of 10T1/2 cells by BP and 3-MC depended upon both concentration and time of exposure. Since both BP and 3-MC are extensively metabolized to polyoxygenated derivatives and conjugates, certain of the metabolites may have acted as antipromoting agents. (21 Refs)

39. USE OF TRANSFECTION TO ANALYZE GENETIC INFORMATION AND MALIGNANT TRANSFORMATION.

Weinberg RA
Center for Cancer Res., Massachussetts Inst. Technology, Cambridge, MA, 02139
Biochim Biophys Acta; 651(1):25-35 1981

Use of the procedure of gene transfer is reviewed. Genetic analysis of cellular genes, including those encoding malignancy, is introduced. Thymidine kinase genes represent a simple model system. The transforming genes of retroviruses represent a complex model. The transforming genes present in cells transformed by non-viral agents illustrate a more complex system: topics discussed include transmission of transforming genes present in chemically-transformed cells, multiplicity of 3-methylcholanthrene-induced transforming genes, range of donor tumor cells carrying biologically active DNA, and use of transfection to study viral leukemogenesis. Transfection used for molecular cloning of selectable genes is discussed with respect to sib selection, identifying the gene via existing linkage to an easily identified sequence, artificial linking of an identifiable sequence to a gene of interest, and plasmid-mediated rescue. Conclusions and prospects for transfection are presented. (85 Refs)

GENERAL REVIEWS AND OTHER RELATED STUDIES

40. MANIFESTATION OF CARCINOGENESIS AS A STOCHASTIC PROCESS ON THE BASIS OF AN ALTERED MITOCHONDRIAL GENOME.

Neubert D, Hopfenmuller W, Fuchs G
Institut fur Toxicologie und Embryopharmakologie, Freien Universitat Berlin, Garystrasse 9, D-1000 Berlin 33, W. Germany
Arch Toxicol; 48(2/3):89-125 1981

Computer calculations are used to show the feasibility of a concept which explains the manifestation of a pathological cell function from a latent state by the phenomenon of extrachromosomal inheritance (through the mitochondrial genome) in mammalian cells. A hypothesis is submitted in which this principle is applied to the process of carcinogenesis. According to this concept, the manifestation of a tum or cell - after the initiation stage - entirely depends on stochastic events, ie, random distribution of mitochondria during cell divisions, with an accumulation of the lesion in a few out of many cells. We feel that this concept comprises a better explanation of many characteristics and peculiarities of the phenomenon of carcinogenesis than do attempts which explain tumor formation as a phenomenon caused by mutation in a nuclear genome. A consideration of the principles presented automatically leads to a number of specific consequences with regard to carcinogenesis. Some of these consequences are discussed. They include: 1. the process of malignant transformation should not be irreversible for all the cells of a progeny; 2. the number of mitochondria in a cell type should be inversely correlated to tumor frequency; 3. the latent period should mainly be determined by the cell division rate and the 'extent' of the initiating event; 4. susceptibility to carcinogenesis may be substantially higher if the number of mitochondria per cell line is increasing or decreasing, ie, during the embryonic and fetal periods; 5. heterogeneous types of cells may arise from a single 'initiated' cell, and 6. the process of malignant transformation should not necessarily be confined to one generation of the species. In addition, experimental approaches to support the submitted concept are suggested. (Author abstract) (91 Refs)

41. TWO INDEPENDENT ASPECTS OF TUMOR PROMOTION.

Berenblum I, Armuth V
Weizmann Inst. Science, Rehovot, Israel
Biochim Biophys Acta; 651(1):51-63 1981

The possibility of separate and independent mechanisms of tumor promotion is explored based on a review of evidence for sites of action within the cell. The multi-stage theory of carcinogenesis is presented. Evidence for two types of promoting action is discussed: that operating at the regulator-gene level and that operating at the level of the cell-surface membrane. Tumor promotion is generally regarded as an epigenetic phenomenon in an initiated cell which permits the phenotypic expression of an altered genotype. Since an influence on the cell's mutation rate or its repair mechanisms would need to operate close in time to initiation, these mechanisms are not widely regarded as likely. Growing evidence suggests that promotion may proceed by the derepression of a neighboring regulator gene brought about by the action of some newly synthesized tumor-specific protein(s). Cell membranes in general and cell-surface membranes in particular have an important role in regulating cellular functions, and a great variety of changes in cell-surface membranes is known to effective in this regard. Lack of cell adhesiveness and of contact inhibition in neoplastic cells have long been recognized as cell-surface phenomena. There is evidence that promoters, particularly phorbol ester promoters, can bind to cell-surface membranes and alter their properties. Induction of plasminogen activator, prostaglandins, enzymes of polyamine biosynthesis, and alterations in cyclic nucleotide levels are known cytoplasmic effects of promoter action. Implications and interrelations of these findings are discussed. (224 Refs)

42. HEREDITARY AND ENVIRONMENTAL FACTORS IN THE CAUSATION OF NEOPLASIA BASED ON STUDIES IN XIPHOPHORUS.

Anders F
Genetisches Institut, Heinrich-Buff-Ring 58-62, D-6300 Giessen, W. Germany
Klin Wochenschr; 59(17):943-956 1981

The genetic information for neoplastic transformation is inherited as a normal part of the genome in all individuals of Xiphophorus. Neoplasia, however, was found only in hybrids between members of different populations and local races. It can be classified in (a) a large group that is triggered by mutagens, (b) a large group triggered by promoters, (c) a small group that develops 'spontaneously', and (d) a small group that is inherited according to Mendelian Laws. The process leading to susceptibility for neoplasia is represented by the disintegration of coadapted gene systems that normally protect the fish from neoplasia. Hybridization is the most effective process that leads to disintegration of the protection gene-systems. Environmental mutagens and promoters (ie carcinogens) may complete disintegration and thus may trigger neoplasia. The phenomenon of introducing susceptibility to neoplasia by means of hybridization has been observed in a large variety of plants and animals. While we have no data on the relation between hybridization and cancer in human beings comparable to those in plants and animals, we put the question whether the many facts on tumor incidence in humans, that do not agree with the concept of the primacy of environmental factors in carcinogenesis may be explained by interpopulational and interracial hybridization in preceding generations. Based on our studies on Xiphophorus we suppose that environmental factors represent only the peak of an iceberg in the multistep process of the causation of neoplasia. The most important steps leading to neoplasia, ie those that bring about susceptibility, are supposed to be hidden in our ancestry. (Author abstract) (87 Refs) (In GER)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. TOXICOLOGICAL ASPECTS OF POLYCYCLIC AROMATIC HYDROCARBONS (PAH).
De Fernicola NA, De Azevedo FA
Divisao de Toxicologia e Ecotoxicologia, Diretoria de Tecnologia e Desenvolvimento, Sao Paulo, Brazil
Rev Bras Saude Ocup; 33(9):62-68 1981
In POR

2. EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.
International Agency for Research on Cancer
International Agency for Res. on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum; 26:1-411 1981

3. STUDIES ON THE ROLE OF ORAL CONTRACEPTIVE USE IN THE ETIOLOGY OF BENIGN AND MALIGNANT LIVER TUMORS.
Mettlin C, Natarajan N
Cancer Control and Epidemiology, Rosewell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Surg Oncol; 18(1):73-85 1981

RADIATION CARCINOGENESIS

4. EXPERIMENTAL RADIATION CARCINOGENESIS: WHAT HAVE WE LEARNED?
Fry RJ
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Radiat Res; 87(2):224-239 1981

5. INFLUENCE OF NONCARCINOGENIC SECONDARY FACTORS ON RADIATION CARCINOGENESIS.
Little JB
Lab. Radiobiology, Harvard Univ., Sch. Public Health, Boston, MA, 02115
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6. MEDICAL IRRADIATION IN JAPAN - STOCHASTIC RISK ESTIMATION AND ITS REDUCTION.
Hashizume T
Div. Physics, National Inst. Radiological Sciences, 9-1 Anagawa 4-Chome, Chiba Shi 260, Japan
Nippon Igaku Hoshasen Gakkai Zasshi; 41(5):445-474 1981
In JPN

7. RADIOACTIVITY IN DRINKING WATER.
Cothern CR
Office of Drinking Water, Environmental Protection Agency, Washington, DC
Radioactivity in Drinking Water. Available from National Technical Information Service, Springfield, VA, as PB81-192833:, 79 pp., 1981.

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

8. EPIDEMIOLOGY OF GASTROINTESTINAL CANCER.
Miller AB
NCIC Epidemiology Unit, Univ. Toronto, McMurrich Building, Toronto, Ontario M5S 1A8, Canada
Compr Ther; 7(8):53-58 1981

9. EPIDEMIOLOGICAL ASPECTS OF ESOPHAGEAL CANCER.
Ruggieri M, Tosato F, De Rocco K, Lepore M, Cipriano E, Paolini A
IV Cattedra di Clinica Chirurgica Generale e Terapia Chirurgica, Universita degli Studi di Roma, Rome, Italy
Recenti Prog Med; 70(5):545-556 1981
In ITA

10. PANCREATIC CANCER.
Cohn I, Hastings PR
Dept. Surgery, Louisiana State Univ., 1542 Tulane Ave., New Orleans, LA, 70112
UICC Tech Rep Ser. Vol. 57, Issue 12, 142 pp., 1981.

11. GENETICALLY DETERMINED SUSCEPTIBILITY TO CANCER.
Marks PA
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Blood; 58(3):415-419 1981

12. ETIOLOGY, ROLE AND DETECTION OF CHROMOSOMAL ABERRATIONS IN MAN.
Fabricant JD, Legator MS
Dept. Preventive Medicine, Div. Environmental Toxicology, Univ. Texas Medical Branch, Galveston, TX, 77550
JOM; 23(9):617-625 1981

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13. INDUSTRIAL CARCINOGENESIS.
Vickers CF
Dept. Dermatology, Univ. Liverpool, Liverpool L69 3BX, England
Br J Dermatol; 105(Suppl21):57-61 1981

14. ENVIRONMENT AND HEALTH (LITERATURE REVIEW).
Khachatrian TS
Dept. Public Health, State Inst. Advanced Training for Physicians, Erevan, USSR
Zh Eksp Klin Med; 21(3):287-292 1981
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15. LIFESTYLE AND CANCER.
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16. ASBESTOS, AN ENVIRONMENTAL POLLUTANT.
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17. REVIEW OF UICC PROGRAM ON SMOKING AND LUNG CANCER.
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Smoking and Cancer Program, UICC, 3 rue du Conseil General, 1205 Geneva, Switzerland
Cancer Forum; 5(1):15-18 1981

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18. EXPERIMENTAL APPROACHES TOWARDS THE BIOCHEMICAL ANALYSIS OF CHEMICAL CARCINOGENESIS.
Laishes BA
McArdle Lab. for Cancer Res., Univ. Wisconsin Medical Sch., Madison, WI, 53706
ACS Symp Ser; 160:197-215 1981

19. FIBRONECTIN AND RELATED TRANSFORMATION-SENSITIVE CELL SURFACE PROTEINS (ONCOLOGY OVERVIEW).
International Cancer Research Data Bank
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Fibronectin and Related Transformation-Sensitive Cell Surface Proteins (Oncology Overview) Chen, L B, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-923001:; OB-81/01:95pp. 1981

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Preneoplastic Lesions of the Mammary Gland (Oncology Overview) Medina, D, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-923002; OB-81/02:134pp. 1981

21. LYMPHOCYTE DIFFERENTIATION: AN ESSENTIAL BASIS FOR THE COMPREHENSION OF LYMPHOID NEOPLASIA.
Magrath IT
Pediatric Oncology Branch, Div. Cancer Treatment, NCI, NIH, Public Health Service, United States Dept. Health and Human Services, Bethesda, MD, 20205
JNCI; 67(3):501-514 1981

MODIFICATION OF CARCINOGENESIS

22. FACTORS STIMULATING AND INHIBITING TUMOR GROWTH IN CARCINOGENESIS.
Kochergina NI, Kosova IP
Res. Lab. Experimental Immunobiology, Moscow, USSR
Usp Sovrem Biol; 91(3):409-418 1981
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23. TWO INDEPENDENT ASPECTS OF TUMOR PROMOTION.
Berenblum I, Armuth V
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24. BURKITT'S LYMPHOMA.
Ziegler JL
NCI, Bethesda, MD, 20205
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25. REVIEW ARTICLE. REGULATION OF EXPRESSION OF THE INTEGRATED RETROVIRUS GENOME.
Weinberg RA, Steffen DL
Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
J Gen Virol; 54(part1):1-8 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

26. THE DEVELOPMENT AND VALIDATION OF MUTAGENICITY SCREENING TESTS.
Durkin PR, Santodonato J
Center for Chemical Hazard Assessment, Syracuse Res. Corporation, Merill Lane, Syracuse, NY, 13210
Tappi; 64(9):153-159 1981

27. SHORT-TERM TEST SYSTEMS FOR POTENTIAL MUTAGENS AND CARCINOGENS: I. MICROBIAL TESTS (ONCOLOGY OVERVIEW).
International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Short-Term Test Systems for Potential Mutagens and Carcinogens: I Microbial Tests (Oncology Overview) Simmon, V F; Peirce, V; eds This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-922903:; OK-81/03:124pp. 1981

28. ANIMAL MODELS OF INTRA-ORAL CHEMICAL CARCINOGENESIS: A REVIEW.
Eveson JW
Dept. Oral Medicine and Pathology, Guy's Hosp., London SE1 9RT, England
J Oral Pathol; 10(3):129-146 1981

29. THE CHROMOSOMES IN HEMATOLOGY.
Berger R
Laboratoire de Cytogenetique, Institut de Recherches sur les Leucemies et les Maladies du Sang, UER d'Hematologie, Hopital Sant-Louis, 2 place du Dr. Fournier, 75475 Paris Cedex 10, France
Cancer Genet Cytogenet; 4(1):69-88 1981

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SERIES CK14 No. 82/03

MARCH, 1982

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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HE 20. 3173/2:

TRANSFORMATION GENE STRUCTURE

1. TRANSFORMING GENES OF RETROVIRUSES: DEFINITION, SPECIFICITY, AND RELATION TO CELLULAR DNA.

Duesberg PH, Bister K
Dept. Molecular Biology, Wendell M. Stanley Hall, Univ. California, Berkeley, CA, 94720
Haematol Blood Transfus; 26:383-396 1981

In this review, onc genes of the rapidly transforming sarcoma and acute leukemia viruses are described and defined. The question is then pursued as to whether the oncogenic specificity of some and lack of specificity of other viruses is due to distinct onc genes or whether one such gene can cause multiple forms of cancer. An additional question addressed is the relationship between viral onc genes and cellular DNA. The final question dealt with is how lymphatic leukemia viruses, which lack known onc genes, may cause cancer. The focus is mainly on avian tumor viruses, because their genetic structures are better defined than those of other viruses. (83 Refs)

2. AVIAN LYMPHOID LEUKOSIS IS CORRELATED WITH THE APPEARANCE OF DISCRETE NEW RNAS CONTAINING VIRAL AND CELLULAR GENETIC INFORMATION.

Hayward WS, Neel BG, Fang J, Robinson HL, Astrin SM
Rockefeller Univ., 1230 York Ave., New York, NY, 10021
Haematol Blood Transfus; 26:439-444 1981

The virus-related RNA and DNA from 23 avian leukosis virus (ALV)-induced tumors (22 lymphomas, 1 fibrosarcoma) was analyzed. The normal 35S and 21S ALV RNAs were present in many of the lymphomas analyzed. Of the 22 lymphomas, 19 (from 14/17 birds) contained new RNA species not found in uninfected cells or in nontransformed infected cells. In all cases where more than one tumor from the same animal was examined, the same new tumor-specific RNA was found. Class I and II RNAs were not detectable with circular DNA(cDNA)rep, a probe representing the entire viral genome; this indicated that these RNAs contain little, if any, viral information other than the 5' sequences and presumably contain cellular sequences. Class III RNA was detected but the intensity of the bands suggested that only a small portion of the information in these RNAs could be virus-specific. Three of the four tumors analyzed by liquid hybridization contained low or undetectable amounts of 35S and 21S RNAs. In each of these tumors, the levels of RNA detected with cDNAss was at least 20-fold greater than that detected with cDNArep. The ss-containing RNA, presumably representing the new tumor-specific RNAs, was present at levels ranging from 100-1,300 copies per cell. The expression of cellular transformation-specific sequences was studied. New tumor-specific restriction fragments, containing both viral and cellular sequences (JF: junction fragments), were present in lymphoma DNA. All tumors from one bird contained the same tumor-specific JF. New tumor-specific JF were found in all tumors analyzed. Four size classes of JF were found to be common to more than one tumor. The presence of a specific JF correlated with the presence of a new tumor-specific RNA in 8/10 birds in which both RNA and DNA were analyzed. The data suggested that expression of viral genes is not required for maintenance of neoplasia and that lymphoma induction seems to occur only when the provirus integrates at one of a limited number of sites on the host cell chromosome. (25 Refs)

3. IDENTIFICATION OF THE AVIAN MYELOBLASTOSIS VIRUS GENOME.

Souza LM, Bergmann DG, Baluda MA
(c/o Baluda) Dept. Microbiology and Immunology, UCLA Cancer Immunology Center, 921 Westwood Blvd., Los Angeles, CA, 90024
Haematol Blood Transfus; 26:429-431 1981

Unintegrated and integrated viral DNA intermediates were characterized; results are summarized. Linear viral DNA isolated from cytoplasm of helper virus (MAV-1 or MAV-2) infected chicken embryonic fibroblasts was distinguished by Hind III restriction endonuclease cleavage. The arrangement of endogenous proviral DNA in the chicken genome was determined prior to avian myeloblastosis virus (AMV) infection. Infections were carried out in vitro and in vivo using AMV-S, AMV-B, and AMV-C stocks. Characterization by restriction enzyme fragmentation, construction of recombinant DNA clones, and hybridization studies is described. Restriction enzyme maps of the presumptive AMV and MAV-1-like genomes are presented. Hybridization studies demonstrated that the AMV genome contains a cellular substitution; physical mapping places this substitution in the region normally occupied by the envelope gene. The substitution may be responsible for leukemogenic potential and defectiveness. Differences between AMV and avian defective transforming viruses are listed. (7 Refs)

4. COMPLETE NUCLEOTIDE SEQUENCE AND ORGANIZATION OF THE MOLONEY MURINE SARCOMA VIRUS GENOME.

Reddy EP, Smith MJ, Aaronson SA
Lab. Cellular and Molecular Biology, NCI, Bethesda, MD, 20205
Science; 214(4519):445-450 1981

The complete nucleotide sequence of a mammalian transforming retrovirus, Moloney murine sarcoma virus, has been determined. MSV, a recombinant virus derived of helper viral and cellular sequences, possesses termini resembling prokaryotic transposable elements. The viral genome has the coding capacity for the Moloney murine leukemia virus gag gene product and contains large deletions in pol and env genes. A large open reading frame encompassing its cell-derived sequences codes for its putative transforming protein. The nature of some of the important domains in the viral genome has been established, and their structure is discussed in relation to their function. (Author abstract) (48 Refs)

5. THE LONG TERMINAL REPEAT OF MALONEY SARCOMA PROVIRUS ENHANCES TRANSFORMATION.

Blair DG, Oskarsson M, McClements WL, Van de Woude GF
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Haematol Blood Transfus; 26:460-466 1981

Enhancement by the long terminal repeat (LTR) of Moloney sarcoma virus (MSV) of transformation by an internal MSV fragment containing the MSV-acquired V-mos sequence in mouse cells was reviewed. DNA sequences containing only V-mos transformed NIH 3T3 cells with an activity 10,000-fold lower than that of HT1 MSV DNA. DNA containing only the 5' or 3' LTR of MSV had no transforming activity. When DNA fragments containing LTR were combined with fragments containing V-mos, the full transforming activity of HT1 MSV DNA was obtained. Mutants of gamma-MSV hybrids retained one of two LTR present in MSV, but lost the second LTR and the V-mos sequences. When the retained LTR was cloned as 'pmlsp' or 'pHT1sp' and transfected with DNA containing V-mos, transformation was enhanced in NIH 3T3 cells. Neither pmlsp nor pHT1sp alone produced any transformation. The cellular genome fragment C-mos did not transform cells unless normal Balb/c sequences 5' to C-mos were replaced by MSV sequences, which included LTR and portions of the gag, pol, and env genes. Env apparently was required for expression of C-mos. (18 Refs)

6. CELLULAR HOMOLOGUE (C-SRC) OF THE TRANSFORMING GENE OF ROUS SARCOMA VIRUS: ISOLATION, MAPPING, AND TRANSCRIPTIONAL ANALYSIS OF C-SRC AND FLANKING REGIONS.

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Proc Natl Acad Sci USA; 78(9,part2):5842-5846 1981

The tumorigenic properties of Rous sarcoma virus are attributable to a 60,000-dalton protein, pp60v-src, encoded by a single viral gene, v-src. A homologous gene, c-src, that contains the information for a 60,000-dalton protein, pp60c-src, has been identified in all tested vertebrate cells. By screening a recombinant DNA library representative of the chicken genome, we isolated two overlapping DNA fragments that contain more than 30 kilobases (kb) of DNA spanning the coding sequences for pp60c-src. This 30-kb region is devoid of moderately or highly repeated sequences and shares homology with the entire viral gene and noncoding sequences 5' of v-src. Although v-src has an uninterrupted coding sequence, c-src is interrupted by a minimum of seven intervening sequences. At least two polyadenylylated RNAs seem to be encoded within the DNA we have isolated. The larger RNA, approx 3.9 kb, is the presumptive c-src mRNA; the smaller transcript of about 2 kb hybridizes to DNA sequences several kb from the 3' end of the v-src/c-src homology area. (Author abstract) (28 Refs)

7. GENERATION OF BALB-MUSV AND HA-MUSV BY TYPE C VIRUS TRANSDUCTION OF HOMOLOGOUS TRANSFORMING GENES FROM DIFFERENT SPECIES.

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Cell; 26(1):129-134 1981

The nature of the cell-derived (bas) sequences of BALB-MuSV, a spontaneous mouse sarcoma virus isolate, was determined. Molecularly cloned bas sequences demonstrated no detectable homology with the onc genes of other mouse transforming viruses, but exhibited a high degree of sequence homology with the ras gene of the rat-derived Harvey murine sarcoma virus (Ha-MuSV) genome. The Ha-MuSV cell-derived sequence (ras) shared a colinear 750 bp region of homology with bas. Moreover, BALB-MuSV transformation was associated with the expression of high levels of a 21,000 dalton protein, immunologically related to the ras gene product, p21. Thus bas and ras represent retroviral transforming gene homologs that were independently transduced by mouse Type C viruses from the genomes of different species. (Author abstract) (41 Refs)

8. PERSISTENCE OF NON-INTEGRATED VIRAL DNA IN BOVINE CELLS TRANSFORMED IN VITRO BY BOVINE PAPILLOMAVIRUS TYPE 2.

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Nature; 293(5835):749-751 1981

The presence and maintenance of bovine papillomavirus 2 (BPV 2) in bovine cells transformed in vitro by BPV 2 was studied. Two of the cell lines (12CON/BPV 2 and 16CON/BPV 2) arose from infection of bovine conjunctiva at the 12th and 16th passage, and another (17PAL/BPV 2) arose from infection of the bovine palate at the 17th passage. High-mol wt DNA was prepared from each cell line at various passages and cleaved with the restriction enzyme EcoRI, HindIII, and HindII. Cleaving with these enzymes produced DNA fragments which co-migrated with fragments produced by cleaving BPV 2 DNA. Each cell line contained multiple copies of the BPV 2 genome, ranging from 33-55 viral genome equivalents per diploid quantity of cell DNA. Cells in each line contained disproportionate amounts of viral DNA. No evidence of virus or viral antigens was found in the three cell lines. These findings constitute the first detection of papillomavirus DNA in in vitro transformed cells of the natural host. These findings could be significant in terms of the analysis of oncogenic virus-cell interactions. The results underline further the difficulty in establishing suitable in vitro tissue culture systems to propagate papillomavirus. (27 Refs)

9. EPISOMAL AND NONEPISOMAL HERPESVIRUS DNA IN LYMPHOID TUMOR CELL LINES.

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Haematol Blood Transfus; 26:197-203 1981

Experiments were carried out on two oncogenic viruses of New World primates Herpesvirus saimiri and Herpesvirus ateles, to study the persistence of the viral DNA in host cells and the transformation of host cells by these viruses. The complete viral genomes are linear duplex DNA that contain a unique segment of L-DNA and two terminal segments of H-DNA. Transformed lymphoid tumor cells contain substantial amounts of viral L- and H-DNA, apparently as nonintegrated circular superhelical episomal DNA; they also yield a viral DNA fraction (after digestion with restriction endonucleases) that is not found in the episomal viral DNA, but the exact nature of this fraction is not yet known. The resistance of viral DNA to certain restriction endonucleases and the measured buoyant density of this DNA in cesium chloride gradients suggests that the viral DNA (both episomal and nonepisomal) is extensively methylated in nonproducer cell lines. This methylation can be reduced by conventional inhibitors of DNA methylation and by the tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate. The significance of the inhibition of methylation by this tumor promoter is not known. (17 Refs)

10. ANALYSIS OF RESTRICTION ENDONUCLEASE FRAGMENTS OF INTRACELLULAR EPSTEIN-BARR VIRUS DNA AND ISOENZYMES INDICATE A COMMON ORIGIN OF THE RAJI, NC-37, AND F-265 HUMAN LYMPHOID CELL LINES.

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Virology; 115(1):115-124 1981

Circular Epstein-Barr virus DNA molecules isolated from different virus-transformed cell lines usually show similar but distinct restriction enzyme cleavage patterns. It is shown here that EBV DNA from the cell line Raji, which is of African Burkitt lymphoma origin, has the same cleavage pattern on digestion with either EcoRI, HindIII, or BamHI as EBV DNA from two more recently established human lymphoid cell lines, NC-37 and F-265, which are presumed to be of nontumor origin. On the other hand, these three EBV DNA isolates are clearly different from DNA of the standard B95-8 strain of the virus as judged by the same criteria. A restriction enzyme cleavage map of the circular EBV DNA from Raji cells has been made to provide a basis for the comparison. The isoenzyme patterns of 14 different marker enzymes were also investigated for the Raji, NC-37, and F-265 lines and found to be closely similar. These data indicate that the NC-37 and F-265 lines are not independent isolates of human lymphoid cell lines. (Author abstract) (31 Refs)

TRANSFORMATION GENE EXPRESSION AND REGULATION

11. MANIFOLD EXPRESSION OF NEW CELLULAR GENES IN HUMAN LYMPHOID NEOPLASIA.

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Proc Natl Acad Sci USA; 78(10):6504-6508 1981

Previous studies performed in our laboratory have shown that a minor single-stranded DNA component (ssDNA) isolated from the bulk of double-stranded nuclear DNA (nDNA) of human, murine, or avian cells consisted mainly of active transcription sites. In the present work, ssDNA isolated from human lymphoid cells, either malignant or not amounted to 1.2-1.4% of the total nDNA. This was labeled with 1251 and utilized as a probe in RNA-driven iterative hybridization and cross-hybridization assays. In all cas es of neoplasia studied, the same subfraction of ssDNA (equivalent to 10-12% of the total ssDNA) from malignant cells could be hybridized with cytoplasmic RNA from malignant cells, whatever their origin: acute lymphoid leukemia cells collected from blood of leukemic patients, local lymphosarcomas, or cells from two established strains grown in suspension, one Epstein-Barr virus positive (Raji strain), the other Epstein-Barr virus negative (Ramos strain). The majority of these tumor-specific DNA sequences could be reassociated with unique-copy DNA from both normal and malignant cells and were not expressed in normal lymphoid cells, including those of an established strain immobilized by Epstein-Barr virus and multiplied in culture. It is concluded that a great number of new transcription units, in the range of 2,500-3,000 per cell genome, were activated after spontaneous malignant transformation of lymphoid cells. (Author abstract) (27 Refs)

12. PROTEOLYTIC PROCESSING OF AVIAN AND SIMIAN SARCOMA AND LEUKEMIA VIRAL PROTEINS.

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Haematol Blood Transfus; 26:409-413 1981

The cleavage of a 110,000 dalton fusion protein of the replication-defective avian acute leukemia virus MC 29 and a gag protein precursor pr65 of Simian sarcoma virus by p15 into discrete smaller proteins is described. A discussion is also presented on how p15 could be used as a tool for mapping transformation proteins. (15 Refs)

13. VIRAL GENE EXPRESSION IN CELLS TRANSFORMED BY SIMIAN SARCOMA VIRUS, AND INFECTIOUS PRIMATE TYPE C RETROVIRUS.

Bergholz CM
No affiliation given
Haematol Blood Transfus; 26:524-526 1981

Studies on the viral gene expression in Simian sarcoma virus (SSV)-transformed virus producing marmoset monkey cells [HF/SSV(SSAV)] and SSV-transformed nonproducer marmoset cell lines (HF/SSV-NP) are described. Using antiserum specific for SSV(SSAV: nontransforming associated virus) p30 and another specific for SSAV envelope proteins, it was demonstrated that anti-SSAV p30 precipitates predominantly polypeptides of approx 30,000 and 60,000-62,000 daltons and, in addition, polypeptides of approx 72,000 and 52,000 daltons. Results of pulse-chase experiments indicated that the 60,000 dalton protein (pr60gag) is processed to yield p30, the major viral core protein. Using antiserum specific for gp70 and p15E/p12E, large amounts of 82,000 dalton polypeptide were precipitated; results of pulse-chase experiments indicated that it is an envelope precursor protein processed to yield p15E and p12E. Two virus-specific phosphoproteins, the pr60gag and p12 were revealed by electrophoresis. No phosphorylated proteins were precipitated by ant iserum specific for SSAV envelope proteins. IgG was phosphorylated in extracts of both HF/SSV(SSAV) and HF/SSAV cells, but not in extracts of HF/SSV-NP cells. Expression of SSAV-related sequences by the SSV provirus was investigated by reacting an SSAV circular DNA with increasing concentrations of RNA extracted from two HF/SSV-NP cell lines. The results indicated that SSAV-related sequences were transcribed but represented a smaller proportion of the total cell RNA relative to virus producing cells. Comparison of max levels of hybridization indicated that less of the SSAV genome is represented in the SSV transcripts relative to RNA in SSAV-infected cells. The failure to detect virus-specific proteins in five HF/SSV-NP cells lines shown to contain SSAV-related cytoplasmic RNA suggested that translation of this RNA may be restricted. (1 Ref)

14. CORRELATED LOSS OF THE TRANSFORMED PHENOTYPE AND PP60SRC-ASSOCIATED PROTEIN KINASE ACTIVITY.

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Haematol Blood Transfus; 26:402-404 1981

NY68 cells were infected with a transformation-defective, temperature-sensitive mutant of Rous sarcoma virus. The protein kinase activity of the viral gene product pp60src declined rapidly when the infected cells were shifted to 42 C (nonpermissive for virus growth). Loss of kinase activity correlated with the reversion of the transformed cells to a normal phenotype (evidenced by changes in cell microfilaments). New protein synthesis was not required for the reversion. (9 Refs)

15. THE TRANSFORMATION-SPECIFIC PROTEIN PP60SRC FROM AN AVIAN SARCOMA VIRUS.

Moelling K, Owada MK, Donner P, Bunte T
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Haematol Blood Transfus; 26:405-408 1981

The isolation, purification, and characterization of Schmidt-Ruppin virus, subgroup D, transformation-specific protein pp60src are reported. The protein was located in the virion membrane but was not accessible to antibodies, surface iodination, or protease. (7 Refs)

16. IN VITRO TRANSLATION OF AVIAN MYELOBLASTOSIS VIRUS RNA.

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J Virol; 40(1):107-117 1981

Avian myeloblastosis virus (AMV)-infected cells contain two viral mRNA's, a genome-sized 34S (7.5-kilobase) mRNA and a 21S (2.5-kilobase) subgenomic mRNA, which contains the AMV-specific sequences (myb sequences). We found that AMV virions packaged both the 7.5-kilobase full-length genomic RNA and the 2.5-kilobase subgenomic RNA. In vitro translation of AMV virion RNA sized by sucrose density gradient centrifugation yielded 76,000-, 56,000-, 48,500-, 47,000-, and 32,000-dalton products. The 76,000-dalton protein was coded for by RNA throughout the gradient, but the peak of activity was at 34S to 35S. The 56,000-, 48,500-, and 32,000-dalton proteins were encoded in a 21S RNA, and the 47,000-dalton protein was encoded in an RNA of approx 24S. The 76,000-dalton protein was identified as Pr76gag, based upon immunoprecipitation with specific antiserum and the presence of the 19* dipeptide. 7-Methylguanosine triphosphate inhibited the syntheses of Pr76gag and the 56,000-, 48,500-, and 32,000-dalton proteins, but not the synthesis of the 47,000-dalton protein. the 56,000-, 48,500-, 47,000-, and 32,000-dalton proteins were not immunoprecipitated by anti-gag, anti-reverse transcriptase, or anti-gp85 antiserum. Two-dimensional peptide maps of the 56,000-and 48,500-dalton proteins indicated that they were unique. In vitro translational products of myeloblastosis-associated virus 1 were also analyzed to aid in the identification of the AMV myb gene product(s); the translational products analyzed included Pr76gag, p60env, and a 56,000-dalton polypeptide which apparently was not identical to the 56,000-dalton AMV translational product, as determined by two-dimensional peptide mapping. Our data indicated that one of these proteins (56,000, 48,500, or 32,000 daltons) may represent the product of the AMV myb gene and, therefore, the putative transforming protein(s) of AMV. (Author abstract) (57 Refs)

17. TWO VIRUS-SPECIFIC RNA SPECIES ARE PRESENT IN CELLS TRANSFORMED BY DEFECTIVE LEUKEMIA VIRUS 0K10.

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J Virol; 40(1):301-304 1981

OK10 is a defective leukemia virus which shares some biological and biochemical properties of avian myelocytomatosis virus (MC29). We investigated the pattern of transcription of OK10 in both quail and chicken cells. In both cell types, OK10 produced two polyadenylated RNA species of 8.6 and 3.5 kilobases, which both contained sequences derived from the 5' end of the genome and also the presumed transforming gene (myc). This is a novel form of expression for defective leukemia viruses of the MC29 subgroup and may indicate that there is an as-yet-unidentified protein produced in OK10-infected cells which may be involved in transformation. (Author abstract) (25 Refs)

18. GENETIC STRUCTURE, TRANSFORMING SEQUENCE, AND GENE PRODUCT OF AVIAN SARCOMA VIRUS UR1.

Wang L-H, Feldman R, Shibuya M, Hanafusa H, Notter MF, Balduzzi PC
Rockefeller Univ., New York, NY, 10021
J Virol; 40(1):258-267 1981

We analyzed the genetic structure and gene products of the newly isolated avian sarcoma virus UR1, which recently has been shown to be replication defective and to contain no sequences homologous to the src gene of Rous sarcoma virus. The sizes of the genomic RNAs of UR1 and its associated help er virus, UR1AV, were determined to be 29S and 35S (5.9 and 8.5 kilobases), respectively, by gel electrophoresis and sucrose gradient sedimentation. RNase T1 oligonucleotide mapping of purified viral RNAs indicated that UR1 RNA contains eight unique oligonucleotides in the middle of the genome and shares four 5'-terminal and three 3'-terminal oligonucleotides with UR1AV RNA. The unique sequences of UR1 and Fujinami sarcoma virus were found to be closely related to each other by molecular hybridization of UR1 RNA with DNA complementary to the unique sequence of Fujinami sarcoma virus RNA, but minor differences were found by oligonucleotide fingerprinting. In the regions flanking the unique sequences, UR1 and Fujinami sarcoma viral RNAs contain distinct oligonucleotides, which are shared with oligonucleotides of the respective helper viral RNAs. Cells transformed with UR1 produce a single 29S RNA species which contains a UR1 unique sequence; this species is most likely the mRNA coding for the transforming protein. In UR1-transformed cells, a phosphoprotein of 150,000 daltons (p150) was detected by immunoprecipitation with antiserum against gag proteins. p150 was associated with a protein kinase activity that was capable of phosphorylating p150 itself, Ig G of antiserum, and a soluble substrate, alpha-casein. This enzyme transferred phosphate exclusively to tyrosine residues of substrates in vitro, but p150 labeled in vivo with 32P contained both phosphoserine and phosphotyrosine. The in vitro kinase reaction was not affected by the presence of cyclic AMP or cyclic GMP and strongly preferred Mn++ over Mg++. Thus, the properties of UR1 protein are almost identical to those of Fujinami sarcoma virus protein. (Author abstract) (26 Refs)

19. CLEAVAGE OF FOUR AVIAN SARCOMA VIRUS POLYPROTEINS WITH VIRION PROTEASE P15 REMOVES GAG SEQUENCES AND YIELDS LARGE FRAGMENTS THAT FUNCTION AS TYROSINE PHOSPHOACCEPTORS IN VITRO.

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Proc Natl Acad Sci USA; 78(9,part2):5847-5851 1981

The transformation-specific polyproteins of avian sarcoma viruses PRCII, PRCII-p, Fujinami sarcoma virus (FSV), and Esh sarcoma virus (ESV) consist of two domains, one derived from a partial viral gag gene and the other representing an apparently cell-derived insert in the defective viral genome. These gag-linked proteins were cleaved with retrovirion protease p15. Cleavage of PRCII-p polyprotein P170, P105 of PRCII, and P140 of FSV occurred within the gag domain and generated fragments of Mr 130,000, 70,000, and 115,000, respectively, containing all of the transformation-specific sequences linked to a remnant of the original gag sequences. ESV P80 was cleaved inside the transformation-specific domain, yielding a Mr 35, 000-38,000 fragment from the NH2-terminal half of the molecule consisting of the entire gag portion and some non-gag sequences and a Mr 48,000 fragment containing most of the transformation-specific sequences. The tyrosine phosphorylation sites of the polyproteins were found in every case in the transformation-specific fragments. The major serine phosphorylation site of ESV P80 was found to reside in the Mr 35,000-38,000 gag-containing fragment, probably within the transformation-specific sequences of that cleavage product. Removal of all of the gag domain of ESV P80 or most of the gag domain in PRCII-p P170, PRCII P105, and FSV P140 does not affect their ability to be phosphorylated by the polyprotein-associated tyrosine-specific protein kinase activities. This observation suggests that the gag sequences of the polyproteins of classes II (PRCII-p, PRCII, and FSV) and III (ESV) avian sarcoma viruses may not be required for this enzymatic function, which appears to be of importance in transformation. (Author abstract) (31 Refs)

20. VIRAL GENE EXPRESSION IN POLYOMA VIRUS-TRANSFORMED RAT CELLS AND THEIR CURED REVERTANTS.

Fenton RG, Basilico C
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J Virol; 40(1):150-163 1981

We have studied transcription of integrated viral DNA sequences in a variety of ts-a polyoma virus-transformed rat cells and cured revertants (which had undergone excision of variable amounts of integrated viral DNA) to characterize the structure of viral mRNA's produced in these lines under conditions in which integrated DNA is stable. Our results indicate that cells containing intact early region sequences, either in single-copy or tandem insertions, produce mRNA's indistinguishable from those observed early in lytic infection; sequences complementary to the polyoma late region were not transcribed from integrated viral DNA. Cured revertants no longer encoded full-length early mRNA's, but produced viral transcripts whose 3' ends mapped at an alternative early region polyadenylic acid attachment site at 99 map units or extended into flanking host sequences. The phenotype of these revertant cells correlated with the abundance of these transcripts, suggesting that the transforming function(s) of polyoma virus controls the cellular phenotype in a dose-dependent manner. Unexpected results were obtained from studies of cells containing tandem repeats of defective viral DNA in which the polyadenylic acid attachment signal at 25.8 map units and surrounding sequences were deleted. In these cases, polyadenylated mRNA's were observed that contained sequences complementary to the early strand of the polyoma late region. These mRNA's (some larger than 8 kilobases) originated at the viral early promoter, extended into the late region, and continued into the early region of the contiguous repeat in the tandem. The multimeric mRNA's produced contained defective early regions in tandem with late region sequences. S1 analysis indicated that whereas the 5' early region sequences of readthrough transcripts were spliced in the usual manner, internal early region repeats were either unspliced or used only one of the small early region splices. When deletions in the viral DNA began 40 base pairs past the AAUAAA sequence at 25.8 map units, no readthrough transcripts were observed. This suggests that sequences nearby the AAUAAA sequence at 26 map units may control transcription termination of the polyoma early region. (Author abstract) (34 Refs)

21. EXPRESSION OF EARLY ADENOVIRUS GENES REQUIRES A VIRAL ENCODED ACIDIC POLYPEPTIDE.

Ricciardi RP, Jones RL, Cepko CL, Sharp PA, Roberts BE
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Proc Natl Acad Sci USA; 78(10):6121-6125 1981

Host-range mutants of adenovirus 5 that contain a defect in region E1A (0-4.5 units) fail to replicate in HeLa cells and to transform rodent cells. In HeLa cells, these mutants synthesize only the two RNAs from E1A that share the same 5' and 3' termini but differ in length by the amount of internal sequence removed by splicing. RNA from wild-type virus, selected by hybridization to DNA from region E1A, translates into polypeptides of Mr 51,000 and 48,000 that are highly acidic in isoelectric focusing gels. These acidic Mr 51,000 and Mr 48,000 polypeptides are encoded by the longer and shorter E1A RNAs, respectively. Two of the host-range mutants, H5hr1 and H5hr2, fail to synthesize the Mr 51,000 polypeptide but do produce the Mr 48,000 polypeptide and a novel polypeptide thought to be a truncated portion of the Mr 51,000 polypeptide. H5hr1 and H5hr2 are hypothesized to have termination codons in sequences found only in RNA encoding the Mr 51,000 polypeptide. This prediction is verified for H5hr1 by DNA sequence analysis. The other three host-range mutants (H5hr3-5) synthesize both acidic polypeptides and are predicted to be missense. These results strongly imply that the Mr 51,000 polypeptide, alone or in combination with the Mr 48,000 polypeptide, is needed to regulate expression of adjacent viral genes during the early phase of adenovirus infection. (Author abstract) (34 Refs)

22. SV40 RECOMBINANT MOLECULES EXPRESS THE GENE ENCODING P21 TRANSFORMING PROTEIN OF HARVEY MURINE SARCOMA VIRUS.

Gruss P, Ellis RW, Shih TY, Konig M, Scolnick EM, Khoury G
Lab. Molecular Virology, NCI, Bethesda, MD, 20205
Nature; 293(5832):486-488 1981

Construction of the simian virus 40 (SV40)-Harvey murine sarcoma virus (Ha-MuSV) recombinants is described. The presence of a Ha-MuSV promoter element preceding the gene encoding p21 was shown. The new promoter element was found to be active not only in cells infected with recombinant but also in cells transformed with Ha-MuSV. (32 Refs)

23. IDENTIFICATION OF A VIRUS-SPECIFIC POLYPEPTIDE ASSOCIATED WITH A TRANSFORMING FRAGMENT (BGLII-N) OF HERPES SIMPLEX VIRUS TYPE 2 DNA.

Docherty JJ, Subak-Sharpe JH, Preston CM
Microbiology Program, Pennsylvania State Univ., University Park, PA, 16802
J Virol; 40(1):126-132 1981

The BglII N fragment of herpes simplex virus Type 2 (HSV-2) DNA (approx 0.58 to 0.63 map unit) was examined for encoded products. Using plasmid pGZ59, which consists of BglII-N cloned in pAT153, in conjunction with hybrid-arrested translation, mRNA selection, and in vitro protein synthesis, we found that the major translated product of this region has an approx mol wt of 37,800. By further mapping, coding sequences for this polypeptide were located within the region of BglII-N representing approx 0.58 to 0.61 genome map unit. To demonstrate immunological specificity, we used staphylococcal A protein immunoprecipitation with rabbit anti-HSV-1 or HSV-2 sera and antigens from HSV-1 or HSV-2 total mRNA translated in vitro and BglII-N-selected mRNA. The results show that the 37,800-dalton polypeptide has HSV-2 immunological specificity, as it is precipitated with anti-HSV-2 sera but not with anti-HSV-1 or control sera. (Author abstract) (20 Refs)

24. EXPRESSION OF SV40 T ANTIGEN POLYPEPTIDES IN CELLS BIOCHEMICALLY TRANSFORMED BY PLASMIDS CONTAINING THE HERPES SIMPLEX VIRUS THYMIDINE KINASE GENE AND THE GENOME OF AN SV40TSA MUTANT.

Kit S, Otsuka H, Qavi H, Trkula D, Dubbs DR
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Int J Cancer; 28(4):485-496 1981

To study the expression of SV40 tsA genomes that had been non-selectively introduced into mouse cells, SV40 tsA207 DNA was cleaved with BamH I and ligated to BamH I-cleaved plasmid pAGO DNA, which contains a functional HSV-I thymidine kinase (TK) gene in the form of a 2 kbp Pvu II fragment inserted at the Pvu II site of pBR322. Recombinant plasmids (11-12 kbp) were isolated and amplified in Escherichia coli K12 strain RRI. Restriction nuclease analyses demonstrated that recombinant plasmids pSB15 and pSB10 contained intact SV40 genomes with the polarity of transcription oriented in the same direction (clockwise) or the opposite direction (counterclockwise), respectively, in relation to that of the HSV-I TK gene. Cla I-cleaved pSB10 and pSB15 DNAs were used to transform LM(TK-) cells to TK+. Serological and disc PAGE analyses showed that clonal lines transformed by these plasmids all expressed the selected marker, SHV-1 TK. Molecular hybridization experiments showed that transformed clonal lines TF pSB10 C7 and TF pSB15 C10 had integrated intact SV40 genomes at one integration site, TF pSB10 C3 had integrated an SV40 genome with a small deletion near the BamH I site, but TF pSB15 C1 had integrated a plasmid from which most of the SV40 nucleotide sequences had been deleted. IF assays with hamster anti-SV40 tumor sera showed that TF pSB10 C7 and TF pSB15 C10 strongly expressed SV40 T antigens in over 90% of the cells, TF pSB10 C3 expressed SV40 T antigens in a minority of the cells, and TF pSB15 C1 did not express SV40 T antigens at all. [35S]-methionine labeling and immunoprecipitation experiments showed that, at 36.5 C: (1) TF pSB10 C7 and TF pSB15 C10 expressed 92K and 20K mol wt species of SV40 T antigens and 50-55K cellular protein; (2) expression of all three was reduced in TF pSB10 C3 cells; and (3) TF pSB15 C1 expressed none of the SV40 T antigens, nor did parental LM(TK-) or TF 8-2 transformed cells (which contained the HSV-1 TK gene but not SV40 DNA). At 40 C, labeling of the 50-55K cellular protein was markedly reduced in TF pSB10 C7 and pSB15 C10 cells. The results suggest that SV40 large T antigen (92K) induces and/or stabilizes the 50-55K cellular protein in these mouse cells. (Author abstract) (53 Refs)

GENETIC AND OTHER HOST FACTORS WHICH MODULATE ONCOGENIC TRANSFORMATION

25. THE DIFFERENT ORIGIN OF PRIMARY AND SECONDARY CHROMOSOME ABERRATIONS IN CANCER.

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Haematol Blood Transfus; 26:160-166 1981

Based upon an analysis of chromosome aberrations in 1,827 cases of human malignancy, a hypothesis (model) is presented to explain the role of chromosome aberrations in the development of malignancy. Primary, active chromosome changes are attributed to the direct interaction between the oncogenic agent and the host cell's genome; these changes are mainly somatic mutations, but may be associated with structural changes visible in the microscope. Secondary, passive changes are believed to arise randomly by nondisjunction and structural rearrangements and to be followed by selection of cells with changes that amplify primary changes so that they appear as nonrandom chromosome patterns. The neoplasms in the 1,827 cases fell into three large categories: myeloproliferative disorders, lymphoproliferative disorders, and solid tumors; these three groups were further subdivided into 15 tumor types. Chromosome aberrations were identified by banding techniques; it was found that specific aberrations clustered selectively on specific chromosomes in each type of neoplasm. (8 Refs)

26. ONTOGENY OF ABELSON MURINE LEUKEMIA VIRUS TARGET CELLS.

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(c/o Rosenberg) Cancer Res. Center, Tufts Univ. Sch. Medicine, 136 Huntington Ave., Boston, MA, 02111
Haematol Blood Transfus; 26:467-471 1981

The appearance of target cells (TC) for Abelson murine leukemia virus (A-MuLV) w as studied during ontogeny by measuring the frequency of TC in fetal liver at various times during gestation. Susceptibility to A-MuLV was measured using the quantitative agar assay. The frequency of susceptible cells was greatest late in gestation, with the max number of transformed foci in 18-19-day livers. Steadily decreasing numbers of foci were found at earlier times. No foci were found in 11-or 12-day livers. The number of foci in the liver dropped after birth. TC could be detected in bone marrow after birth. Infection of mixed fetal liver/adult marrow cultures indicated that failure to detect TC in early stages was due to a lack of TC, rather than to factors suppressing transformation. Transformed cells were lymphoid cells with large nuclei and one or more nucleoli. Many of the cells from adult bone marrow carried Ig and terminal deoxynucleotidyl transferase (TdT). Neonatal liver cells also carried Ig and TdT. Late fetal liver cells carried Ig, but not TdT. Early fetal liver cells carried TdT, but only reduced Ig. Changes in TdT and Ig expression apparently reflect shifts in the TC population during ontogeny. (24 Refs)

27. GENETICS OF SUSCEPTIBILITY TO RADIATION-INDUCED LEUKEMIA. MAPPING OF GENES INVOLVED TO CHROMOSOMES 1, 2, AND 4, AND IMPLICATIONS FOR A VIRAL ETIOLOGY IN THE DISEASE.

Meruelo D, Offer M, Flieger N
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J Exp Med; 154(4):1201-1211 1981

The genetics of susceptibility to radiation-induced leukemia in (A/J x B10)F2 mice were defined and the genes involved were localized. A major locus conferring resistance to fractionated irradiation (Cs-137; 180 rad/wk for 4 wk) induction of leukemia was mapped in chromosome 2 (Ril-1). Loci next to xenotropic murine leukemia virus (MuLV) envelope-related cell-surface antigens (XenCSA) on chromosome 4 (Ril-3) and Pep-3 on chromosome 1 (Ril-2) also influenced susceptibility to the leukemia. Leukemia incidence on day 250 after last irradiation was 86% and 90% in mice lacking the phenotypes Ly-6.2 or Ly-11.2, respectively, on chromosome 2. Effects related to genes linked to Ly-15.2R and Pep-3 loci were less important: the number of phenotype-nonleukemic animals 300 days after irradiation were 29% (phenotype 15.2/15.2) and 15% (Pep-3 phenotype AA). Ril-1 is located in a chromosomal site rich in thymus differentiation-specific loci; a linkage of Ril-1 and Ly-11 suggests that this region of chromosome is not silent to the inductive effects of fractionated irradiation. Tissue-specific activation of endogenous viruses may be explained by dependency on differentiation-specific steps. (40 Refs)

28. DIVERSE FAMILIAL MALIGNANT TUMORS AND EPSTEIN-BARR VIRUS.

Purtilo DT, Liao SA, Sakamoto K, Snyder LM, DeFlorio D, Bhawan J, Paquin L, Yang JP, Hutt-Fletcher LM, Muralidharan K, Raffa P, Saemundsen AK, Klein G
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Cancer Res; 41(11,part1):4248-4252 1981

Continued monitoring of a family for new malignant tumors has revealed diverse immunological and neoplastic disorders during a 15-yr period. In 1966, the proband developed lymphoma. In 1975, his antibody titers to Epstein-Barr virus (EBV) became elevated, an again, he developed a malignant lymphoma. He also had borderline hypo-Ig A, died of glioblastoma multiforme in 1977, and at autopsy, had adenomatous colonic polyps. His eldest brother has normal Ig levels, but developed immune thrombocytopenia in 1973 and had elevated EBV antibody titers in 1980. Another brother had hypo-Ig A, thymoma in 1965, and adenomas and adenocarcinoma of the colon. Two other brothers succumbed to glioblastoma in 1968 and 1969. The father of the proband had bronchiectasis in 1952, hypo-Ig M documented in 1972, and elevated EBV antibody titers 5 yr preceding development of a malignant lymphoma. The latter contained 10 EBV genome equivalents/cell by EBV viral DNA/DNA reassociation kinetics analysis. The proband's grandmother had died of an Ig G-secreting myeloma in 1977, and his grandfather had borderline low Ig M, elevated EBV antibody titers, and hypopharyngeal carcinoma in 1980. Predisposition to oncogenesis in this family was probably inherited. (Author abstract) (26 Refs)

29. CHROMOSOME 14 MARKERS IN TWO EPSTEIN-BARR VIRUS (EBV)-TRANSFORMED LYMPHOBLASTOID CELL LINES OF NORMAL ORIGIN DIFFER FROM THE BURKITT LYMPHOMA (BL)-ASSOCIATED 14Q+ MARKER.

Manolov G, Manolova Y, Klein G, Levan A, Kieler J
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Cancer Genet Cytogenet; 4(2):179-184 1981

Two among 10 Epstein-Barr Virus (EBV)-transformed lymphoblastoid cell lines contained a 14q+ marker in a low frequency of the cells (2 and 9%). By means of 'mesome-prosome' analysis of the G-band patterns of these markers; it was established that the additional chromosome segments of these two 14q+ markers came from chromosomes 3 and 5, respectively, and not from chromosome 8 as in the 14q+ marker of Burkitt lymphoma. Chromosome 8 was not involved at all in any changes in the 10 lymphoblastoid cell lines studied. (Author abstract) (19 Refs)

30. COINCIDENCE OF CYTOGENETIC MARKERS IN FOUR MURINE CELL LINES.

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Cancer Genet Cytogenet; 4(2):169-177 1981

Foreign body tumorigenesis was induced by the sc implantation of a plastic or glass cylinder in BALB/c mice; the inoculation of human neoplastic cells significantly increased the incidence of these anaplastic sarcomas. Of 15 tumors studied, 4 presented the same markers: 1 induced with and 3 without human neoplastic cell inoculation within the foreign body. The markers observed were double minutes (DM), a long acrocentric marker (MLA), and a metacentric marker (MM). The DM are a number of small often tiny chromosomal structures appearing in pairs together with chromosomes of ordinary size. MLA is a long acrocentric derived from a translocation in tandem between chromosomes No 1 and No 16. MM is due to centric fusion of two chromosomes No 10. Numerical anomalies consisted of gains of the same chromosomes types. It is postulated that these coincident findings are related to the foreign-body tumorigenesis. (Author abstract) (23 Refs)

EXPERIMENTAL MODULATION OF ONCOGENIC TRANSFORMATION

31. TRANSFORMING GROWTH FACTORS (TGFS) PRODUCED BY TUMOR CELLS (MEETING ABSTRACT).

Todaro GJ
National Cancer Institute, Frederick, MD, 21701
In Vitro; 17(3):213 1981

Cells tranformed by RNA-containing tumor viruses, as well as certain human tumor cells in culture (sarcomas, carcinomas and melanomas), release potent growth stimulating peptides into the culture medium. These proteins are acid and heat stable, produce profound morphologic changes in rat and human fibroblasts and enable normally anchorage-dependent cells to grow in semi-solid medium. Removal of the factors results in a reversion of cell phenotype. The larger TGF has an apparent mol wt of 20,000-23,000 daltons, while the smaller forms range from 7,000-10,000 daltons. The initial effect on cells of each of the forms involves an interaction with epidermal growth factor (EGF) cell membrane receptors. They compete with 125I-EGF for binding sites on the receptor. The EGF receptor is phosphorylated on tyrosine residues as a result of TGF binding; certain lower mol wt proteins also are phosphorylated following TGF binding. TGFs from both rodent and human cells have been purified by gel filtration, ion exchange chromatography and high pressure liquid chromatography; they are active in producing colony formation and the transformed phenotype at less than 1 ng/ml. Since tumor cells produce TGFs and have receptors that enable them to respond, it is suggested that these peptides play a role in facilitating the growth and progression of tumors under natural conditions. (no Refs)

32. TRANSFORMING GROWTH FACTORS - CHARACTERIZATION OF TWO CLASSFS OF FACTORS FROM BOTH NEOPLASTIC AND NON-NEOPLASTIC TISSUES (MEETING ABSTRACT).

Roberts AB, Anzano MA, Frolik CA, Sporn MB
National Cancer Institute, Bethesda, MD, 20205
Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

We report here that transforming growth factors (TGF's) from several sources fractionated by chromatography on Bio-Gel P-30 can be separated into two distinct classes of growth factors following high pressure liquid chromatography on microBondapak C18 columns using gradients of acetonitrile and water containing 0.1% trifluoroacetic acid. One class has properties similar to those originally described for sarcoma growth factors. This class of TGF's elutes from microBondapak C18 earlier than epidermal growth factor (EGF), used as a marker, and is characterized by competition with EGF for membrane receptor sites and by its ability to induce colony formation in soft agar. The second class of TGF's elutes from microBondapak C18 later than the EGF marker and is characterized by its ability to enhance EGF binding in a radioreceptor assay, and an apparent requirement for EGF for activity in the soft agar growth assay. The low intrinsic colony-forming activity of this new class of TGF's is amplified several hundred fold by the addition of 2 ng/ml EGF, which by itself also has only weak colony-forming activity. Assayed in the presence of EGF, the new class of EGF-dependent TGF's from murine sarcoma virus-transformed mouse 3T3 cells represents over 80% of the total colony-forming units of the 6-12K region of the Bio-Gel P-30 chromatogram. The observation that EGF acts synergistically with certain TGF's places new emphasis on the role of EGF as a controlling factor in neoplastic progression and possibly other proliferative states such as wound healing. (1 Ref)

33. NEW CLASS OF TRANSFORMING GROWTH FACTORS POTENTIATED BY EPIDERMAL GROWTH FACTOR: ISOLATION FROM NON-NEOPLASTIC TISSUES.

Roberts AB, Anzano MA, Lamb LC, Smith JM, Sporn MB
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Proc Natl Acad Sci USA; 78(9,part2):5339-5343 1981

Proteins potentiated by epidermal growth factor (EGF) to induce a transformed phenotype in non-neoplastic rat kidney fibroblasts in cell culture have been isolated from many non-neoplastic tissues of the adult mouse, including submaxillary gland, kidney, liver, muscle, heart, and brain. They resemble previously described transforming growth factors (TGFs) isolated from neoplastic cells as follows: they are extractable by acid/ethanol and are acid-stable, low mol wt (6,000-10,000) polypeptides requiring disulfide bonds for activity, and they cause anchorage-independent growth of non-neoplastic indicator cells that will not grow in soft agar in their absence. Partial purification of these TGFs from submaxillary glands of male mice shows that they are distinct from EGF. Unlike previously described extracellular TGFs, but like certain cellular TGFs from neoplastic cells, they are potentiated by EGF in their ability to promote anchorage-independent growth. The isoelectric point of the submaxillary gland TGF protein is near neutrality. Chromatography on Bio-Gel P-30 followed by high-pressure liquid chromatography has resulted in a 2 2,000-fold overall purification. The most purified protein is active in inducing growth in soft agar in 1 ng/ml when assayed in the presence of EGF. The data add further evidence to the concept that neoplasia may result from a quantitative, rather than qualitative, alteration in non-neoplastic biochemical processes. (Author abstract) (25 Refs)

34. SPECIFIC BINDING OF TRANSFORMING GROWTH FACTOR CORRELATES WITH PROMOTION OF ANCHORAGE INDEPENDENCE IN EGF RECEPTORLESS MOUSE JB6 CELLS.

Colburn NH, Gindhart TD
Lab. Viral Carcinogenesis, NCI, Frederick, MD, 21701
Biochem Biophys Res Commun; 102(2):799-807 1981

Promotion of anchorage independence by a transforming growth factor is reported. JB6 mouse epidermal cells were exposed in vitro to 12-O-tetradecanoyl-phorbol-13-acetate (TPA: 1.6 x 10(-8) M), epidermal growth factor (EGF: 2 or 20 nanog/ml), or transforming growth factor (TGF: 5 ug/ml) derived from a human rhabdomyosarcoma line. Binding was measured using 125I-labeled EGF and TGF. Some clones of JB6 cells, such as clone 41, were sensitive to both EGF and TPA, while others were resistant to both. Sensitivity was measured by colony formation in 0.33% agar. Most of the colonies produced by TPA, EGF, or TGF gave rise to transformed cell lines which formed colonies in agar without inducer. A TPA-resistant derivative cell line of clone 41, R219, did not bind EGF specifically. Anchorage independence could be induced in R219 by TPA or TGF, but not by EGF. These cells appeared to have a class of binding sites specific for TGF in addition to sites binding EGF. The EGF sites, which also bind TGF, evidently were not necessary for transformation by TGF. (16 Refs)

35. THE ROLE OF THYROID HORMONE IN RADIATION AND CHEMICALLY INDUCED ONCOGENESIS (MEETING ABSTRACT).

Borek C, Guernsey DL, Ong A
Department of Radiology, Columbia University, College of Physicians and Surgeons, New York, NY, 10032
In Vitro; 17(3):203 1981

Neoplastic transformation in vitro by x-rays and chemical carcinogens has established the direct oncogenic potential of radiation and chemicals in mammalian cells. Little is known whether hormones, normally present in mammalian serum, can affect this response. Using short-term cultures of diploid hamster embryo cells, and the heteroploid mouse cell line C3H 10T1/2 we studied the effect of triiodothyronine (T3) on transformation. We have found that in both cell types the removal of thyroid hormone from serum-supplemented culture medium (using AG1-X10 resin) inhibits radiation and chemically induced transformation while having no effect on cellular growth rate or survival. When T3 alone is added to thyroid-depleted medium at 10(-7) M, transformation frequency induced by radiation is expressed at a similar frequency as in the presence of culture medium supplemented with untreated serum. We find that exposing the cell s to T3 ranging from 10(-11) M to 10(-7) M results in radiation transformation which is dose dependent. Thyroid hormone is essential for the induction and/or expression of x-ray-induced transformations. Recent findings using Benzo-a-pyrene instead of x-rays as the oncogenic agent, indicate that in the absence of T3 there is no transformation and that T3 is required for the induction and/or expression of neoplastic transformation by the chemical carcinogen. (no Refs)

36. CRUCIAL ROLE OF THYROID HORMONE IN X-RAY-INDUCED NEOPLASTIC TRANSFORMATION IN CELL CULTURE.

Guernsey DL, Borek C, Edelman IS
Dept. Physiology and Biophysics, Univ. Iowa Coll. Medicine, Iowa City, IA, 52242
Proc Natl Acad Sci USA; 78(9,part2):5708-5711 1981

Incubation of mouse embryo fibroblasts (C3H/10T1/2) in media depleted of thyroid hormone for 1 wk rendered the cell completely resistant to the transforming action of an x-ray dose, 4 grays, that yields transformation frequencies (no. foci per surviving cells) of approx 10(-3) in media supplemented with triiodothyronine (T3) (1 nM). Studies on the timing of the additions or removal of the hormone indicate that T3 was maximally effective when added 12 hr before irradiation and that progression from the time of irradiation to the appearance of foci (6 wk) was independent of the presence or absence of the hormone. The dependence of x-ray-induced transformation on the concentration of T3 in the medium was virtually the same as that for augmentation of Na+, K+ -ATPase activity. The latter effect was used as a measure of T3 induction of protein synthesis. A further indication of the involvement of protein synthesis in the process is the abolition of T3-and x-ray-dependent transformation by cycloheximide at a concentration (100 ng/ml) that inhibits 50% of protein synthesis. We propose that thyroid hormone induces the synthesis of a host protein that is an obligatory participant in x-ray-mediated transformation. (Author abstract) (17 Refs)

37. REGULATION OF HUMAN T-CELL PROLIFERATION: T-CELL GROWTH FACTOR AND ISOLATION OF A NEW CLASS OF TYPE-C RETROVIRUSES FROM HUMAN T-CELLS.

Gallo RC, Poiesz BJ, Ruscetti FW
NCI, Bethesda, MD, 20014
Haematol Blood Transfus; 26:502-514 1981

Recent results with human T-cell growth factor (TCGF), the various T cell systems, and the isolation of a new type-C retrovirus released from growing T-cells from some of these T-cell neoplasias are summarized. Unlike normal T-cells, neoplastic mature T-cells respond directly to TCGF without prior lectin or antigen in vitro activation. Transformed T-cell lines exhibit phenotypic characteristics consistent with the neoplastic cells of their disease of origin. A new retrovirus, human T-cell lymphoma-leukemia virus (HTLV) was isolated from fresh and cultured cells from two patients, each with a variant of a cutaneous T -cell lymphoma. Further studies showed that HTLV was not significantly related to any known animal retrovirus, is not an endogenous (genetically transmitted) virus of man, and at present is only associated with fresh or cultured T-cells from patients with the T-cell neoplasia. The results suggest that HTLV infected some mature T-cells of some people and may be involved in some neoplasias involving these cells. (33 Refs)

38. MODIFICATION OF BENZO(A)PYRENE-INDUCED CELLULAR TRANSFORMATION OF C3H/10T1/2 CELLS BY DEXAMETHASONE AND PREGNENOLONE-16ALPHA-CARBONITRILE (MEETING ABSTRACT).

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In Vitro; 17(3):223 1981

Most chemical carcinogens exist in the environment in an unreactive form and require metabolic activation to exert their biological activity. Manipulation of the microsomal enzymes has been proposed as a mechanism for controlling carcinogenesis. In this study two compounds, dexamethasone (DEX) and pregnenolone-16alpha-carbonitrile (PCN), are potent inducers of microsomal enzymes in vivo. Since these enzymes are responsible for the metabolism of carcinogens, the effects of these compounds were studied to determine whether increased enzyme activity was correlated with cellular transformation. Both DEX and PCN were found to induce AHH activity in the C3H/10T1/2 cells by about 2 fold and both compounds increased the rate of metabolism of benzo(a)pyrene to water-soluble products. The steroids however had opposite effects on transformation. DEX inhibited cellular transformation by about 65% at 23 uM concentration. PCN, however, was found to increase the frequency of transformation by more than 100%. Therefore, enhanced AHH activity and metabolism does not necessarily lead to enhanced transformation since other pathways of metabolism, carcinogen detoxification, or repair processes may be involved. (no Refs)

39. CARCINOGEN-MEDIATED AMPLIFICATION OF VIRAL DNA SEQUENCES IN SIMIAN VIRUS 40-TRANSFORMED CHINESE HAMSTER EMBRYO CELLS.

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Proc Natl Acad Sci USA; 78(10):6144-6148 1981

Exposure of simian virus 40 (SV40)-transformed Chinese hamster embryo cells to various chemical and physical carcinogens induced SV40 DNA synthesis. Although the carcinogen-mediated amplification of SV40 DNA is regulated by the viral A gene, the induction of viral DNA synthesis does not result in the rescue of infectious virus or the formation of complete viral DNA molecules. Instead, a heterogenous collection of DNA molecules containing SV40 sequences was generated by treatment with 7,12-dimethylbenz[a]anthracene. Restriction enzyme analysis of the amplified DNA molecules in the Hirt supernatant showed that not all sequences in the integrated SV40 inserts are present. The possibility that amplification of SV40 sequences is a reflection of a general gene-amplification phenomenon mediated by carcinogens is discussed. (Author abstract) (29 Refs)

40. GENETIC APPROACHES TOWARD ELUCIDATING THE MECHANISMS OF TYPE-C VIRUS-INDUCED LEUKEMIA.

Aaronson SA, Barbacid M, Dunn CY, Reddy EP
Lab. RNA Tumor Viruses, NCI, Bethesda, MD, 20014
Haematol Blood Transfus; 26:455-459 1981

The mechanisms of induction of leukemia by murine type-C viruses was studied in newborn NIH/Swiss mice. Inoculations of 5 x 10(4) XC pock forming units of either Rauscher (R) or Moloney (M) murine leukemia virus (MuLV) produced gross enlargement of spleen and lymph nodes as early as 10-11 wk. RMuLV produced spleen enlargement and sometimes liver and peripheral or visceral lymph node enlargement. MMuLV produced thymus enlargement in most animals, and frequently affected other lymphoid organs. MMuLV-induced tumors were of T cell origin, as indicated by presence of Thy1 antigen and absence of Fc or C3 receptors. RMuLV-induced tumors were of B cell lineage, as indicated by presence of Fc receptors and absence of Thy1 antigen. Recombinant forms between oncogenic and nononcogenic type-C viruses were produced in wild mouse embryo cells of line WM-C. These recombinants contained genetic information in varying amounts from both parental viruses and exhibited varying degrees of oncogenicity. Results indicate that target cells for transformation by RMuLV and MMuLV contain specific markers distinguishing them from other lymphoid elements. The necessity of active virus replication for tumorigenesis by murine type-C viruses is suggested. (19 Refs)

41. EFFECT OF THE TUMOR PROMOTER PHENOBARBITAL ON MEMBRANE-MEDIATED PROPERTIES OF ADULT RAT LIVER-DERIVED EPITHELIAL CELLS IN CULTURE (MEETING ABSTRACT).

Shimada T, Kreiser DM, Williams GM
Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
In Vitro; 17(3):224 1981

We have reported a promoting action of phenobarbital on the transformation of adult rat liver (ARL) epithelial cells in culture. We report here various other biological effects of phenobarbital (PB) which mimic induction of transformation on ARL cells. A clonal line of ARL cells, which was proved to be nontumorigenic when examined for transformation markers, was seeded at a density of 1.2 x 10(4) cells/cm2 in Williams Medium E supplemented with heat-inactivated fetal bovine serum at 10% (WME:HIFBS(10)) with gentamicin at 50 ug/ml. Cells were fed with WME:HIFBS10 containing 10(-4) M PB 2 x a wk starting 24 hr after seeding and subcultured once a wk at the same seeding density. Cells that received multiple treatments of PB showed a 10-20% increase in cell population at each subculture up to 10 treatments, and continued to increase in 2-Deoxy-D-glucose (2DG) uptake in the absence of PB by as much as 77% after 2 2 treatments. On the other hand, single PB treatment of ARL cells did not enhance 2DG uptake. Neither single nor multiple treatments with PB induced anchorage independency in ARL cells. It is suggested that the alteration of plasma membrane properties by PB, as in vivo could be the mechanism of the tumor promoting activity of PB. (2 Refs)

42. FELINE LEUKEMIA VIRUS NONPRODUCER LYMPHOSARCOMAS OF CATS AS A MODEL FOR THE ETIOLOGY OF HUMAN LEUKEMIAS.

Hardy WD, McClelland AJ, Zuckerman EE, Snyder HW, MacEwen EG, Francis D, Essex M
No affiliation given
Haematol Blood Transfus; 26:492-494 1981

Immunological and epidemiological studies of feline lymphosarcoma (LSA) are summarized. Immunofluorescent antibody assay, immunodiffusion, tissue culture isolation, and radioimmunoassay were used to test 507 casts with LSA for feline leukemia virus (FeLV). FeLV-positive LSA was found in 360 cats; the remaining 147 had nonproducer (NP) LSA. No FeLV proteins or infectious viruses were detected in NP LSA. However, the FeLV-induced tumor specific oncovirus-associated cell membrane antigen was detected on the surface of both NP and FeLV positive LSA cells. Of 1,612 FeLV-exposed and -unexposed cats observed for development of LSA, 0/1,074 unexposed cats (observed av 3 yr/cat) developed LSA; 149/538 exposed cats (observed av 4.4 yr/cat) were persistently infected. LSA developed in 41 cats, 30 FeLV positive and 11 NP LSA. Difference in rate of NP LSA in FeLV-exposed and -unexposed cats was significant (p less than 0.001). FeLV appears to be the etiologic agent of feline LSA regardless of FeLV status. Mechanisms by which RNA- and DNA-containing viruses induce tumors are discussed. Feline NP LSA could be a useful model for elucidating mechanisms of oncovirus transformation. (12 Refs)

43. FOCUS FORMATION AND NEOPLASTIC TRANSFORMATION BY HERPES SIMPLEX VIRUS TYPE 2 INACTIVATED INTRACELLULARLY BY 5-BROMO-2'-DEOXYURIDINE AND NEAR UV LIGHT.

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Dept. Comparative Medicine and Biochemistry, Johns Hopkins Medical Inst., Baltimore, MD, 21205
J Virol; 40(1):289-300 1981

The induction of focus formation in low serum and of neoplastic transformation of Syrian hamster embryo cells was examined after the expression of herpes simplex virus Type 2 functions. Syrian hamster embryo cells infected at a high multiplicity (5 PFU/cell) with 5-bromo-2'-deoxyuridine-labeled herpes simplex virus Type 2 (11% substitution of thymidine residues) were exposed to near UV light irradiation at various times postinfection. this procedure specifically inactivated the viral genome, while having little, if any, effect on the unlabeled cellular DNA. Focus formation in 1% serum and neoplastic transformation were observed in cells exposed to virus inactivated before infection, but the frequency was enhan ced (15-to 27-fold) in cells in which the virus was inactivated at 4 to 8 hr postinfection. Only 2 of 45 independently isolated foci were capable of establishing tumorigenic lines. The established lines exhibited phenotypic alterations characteristic of a transformed state, including reduced serum requirement, anchorage-independent growth and tumorigenicity. They retained viral DNA sequences and, even at relatively late passage, expressed viral antigens, including ICP 10. (Author abstract) (44 Refs)

44. INDUCTION OF GENE MUTATION IN AND CELL TRANSFORMATION OF MAMMALIAN CELLS BY MODIFIED PURINES: 2-AMINOPURINE AND 6-N-HYDROXYLAMINOPURINE.

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Proc Natl Acad Sci USA; 78(9,part2):5685-5689 1981

A classical mutagen in prokaryotic systems, 2-Aminopurine is inactive as a carcinogen in two animal species. To determine the basis for this discrepancy in the correlation between carcinogenesis and mutagenesis, the ability of 2-aminopurine to induce somatic mutation and neoplastic transformation concomitantly in the same cellular system was examined. 6-N-hydroxylaminopurine, a related modified purine that is a mutagen and a carcinogen, was also studied. 2-Aminopurine was a mutagen in Syrian hamster embryo cells, but its activity was very weak. The max induced mutation frequency with either of two mutational markers was only 7 x 10(-6) mutants per surviving cell. 2-Aminopurine also induced morphological transformation of the cells under the same conditions, but the frequency was only approx 0.04% per surviving colony. Neoplastic transformation of the cells after 2-aminopurine treatment was not observed in these experiments. These results indicate that 2-aminopurine is, at best, a weak transforming agent. The lack of carcinogenic activity in vivo with 2-aminopurine is consistent with these observations. In contrast to the results with 2-aminopurine, 6-N-hydroxylaminopurine was very effective mutagen in these cells (up to 10(-3) mutants per survivor) and induced morphological transformation of the cells in a dose-dependent manner. Furthermore, neoplastic transformation was induced by this nucleic acid base analog, the correlation of mutagenic activity with transforming ability of these two modified purines supports a relationship between mutagenesis and carcinogenesis. However, relative to other carcinogens, there is a quantitative difference in the ability of 6-N-hydroxylaminopurine to induce cell transformation and mutation. For example, in benzo[a]pyrene-treated cultures, the ratio of the frequency of induced morphological transformation to that of somatic mutation was approx 100, whereas for 6-N-hydroxylaminopurine-treated cultures, the ratio of transformation to mutation was only 3-12.5. This indicates that 6-N-hydroxylaminopurine is less potent than benzo[a]pyrene in inducing transformation when compared at equal mutagenic potency. This is consistent with our hypothesis that cell transformation, and possibly cancer, occurs predominantly as the result of a mutation at the chromosome level rather than a gene mutation. (Author abstract) (27 Refs)

BIOCHEMICAL AND MOLECULAR BIOLOGICAL STUDIES OF TRANSFORMED PHENOTYPE

45. CHARACTERIZATION OF ANTIGENS IN SSV NONPRODUCER CELLS.

Thiel HJ, Matthews T, Broughton E, Butchko A, Bolognesi D
Dept. Surgery, Medical Center, Duke Univ., Durham, NC, 27710
Haematol Blood Transfus; 26:520-523 1981

In an attempt to identify putative transformation specific information coded by simian sarcoma virus (SSV), goat cells nonproductively transformed by SSV (SSV-NP) were isolated and inoculated several times as live cells into the same goat. The resulting hyperimmune serum (SSV-NP serum) was reacted in radioimmunoprecipitation against different transformed and nontransformed cell lines. After labeling SSV-NP cells with 3H-glucosamine and 35S-cysteine using a 7 hr pulse followed by a 14 hr chase, the respective tissue culture supernatants were immunoprecipitated with SSV-NP serum. The SSV-NP serum reacted specifically with two different molecules in SSV-NP cells, a SSV transformation-specific glycoprotein (SSV TrS-gp) and p65, which probably represents a modified gag-precursor. (7 Refs)

46. CHARACTERIZATION OF SITES FOR TYROSINE PHOSPHORYLATION IN THE TRANSFORMING PROTEIN OF ROUS SARCOMA VIRUS (PP60V-SRC) AND ITS NORMAL CELLULAR HOMOLOGUE (PP60C-SRC).

Smart JE, Oppermann H, Czernilofsky AP, Purchio AF, Erikson RL, Bishop JM
Cold Spring Harbor Lab., Cold Spring Harbor, NY, 11724
Proc Natl Acad Sci USA; 78(10):6013-6017 1981

The transforming protein of Rous sarcoma virus (pp60v-src) and its normal cellular homologue (pp60c-src) appear to be protein kinases that phosphorylate tyrosine in a variety of protein substrates. In addition, pp60v-src and pp60c-src are themselves phosphorylated on serine and tyrosine. It is likely that these phosphorylations serve to regulate the function(s) of pp60v-src and pp60c-src. We have therefore characterized the sites of tyrosine phosphorylation in the two proteins. Tyrosine phosphorylation of pp60v-src in infected cells occurs mainly (if not entirely) at residue 419 in the deduced amino acid sequence of the protein. Surrounding this residue is the sequence Leu-Ile-Glu-Asp-Asn-Glu-Tyr(P)-Thr-Ala-Arg. This peptide is distinguished by the fact that three out of the four amino acids that precede the phosphorylated tyrosine are acidic in nature. These results define what may prove to be a widely used site for tyrosine phosphorylation in the regulation of cellular function. The same site was phosphorylated when partially purified pp60v-src was used in a phosphotransfer reaction in vitro. The results with pp60c-src were more complex. the site of tyrosine phosphorylation in vitro appeared to be the same as that found in pp60v-src. By contrast, phosphorylation of pp60c-src in vivo apparently occurred at a different, and currently unidentified, tyrosine residue. It is therefore possible that pp60v-src and pp60c-src respond differently to regulatory influences in the intact cell. (Author abstract) (34 Refs)

47. PHOSPHORYLATION PATTERNS OF TUMOR ANTIGENS IN CELLS LYTICALLY INFECTED OR TRANSFORMED BY SIMIAN VIRUS 40.

Van Roy F, Fransen L, Fiers W
Lab. Molecular Biology, State Univ. Ghent, B-9000 Ghent, Belgium
J Virol; 40(1):28-44 1981

The phosphorylation sites of simian virus 40 (SV40) large tumor (T) antigens have been analyzed by partial proteolysis peptide mapping and phosphoamino acid analysis of the resulting products. At least four sites were found to be phosphorylated. An amino-terminal part of the molecule contained both phosphoserine and phosphothreonine. One phosphothreonine residue was located in the proline-rich carboxy-terminal end of the molecule, either at position 701 or at position 708. The mutant dl1265, which is defective in adenovirus helper function, lacked this phosphorylation site. In addition, the carboxy-terminal part of the molecule contained phosphoserine at a more central position. T-antigen-associated proteins of SV40-

transformed cells (nonviral T; 51,000 to 55,000 daltons) also contained multiple phosphorylation sites involving at least two serine residues in mouse antigens and an additional threonine residue in rat, human, and monkey antigens. The latter residue and at least one phosphoserine residue were located near one terminus of the human NVT molecule. We did not find any evidence for phosphorylation of tyrosine residues in any of the multiple species of either large T or nonviral T molecules. Several forms of large T antigens were extracted from both SV40-transformed and SV40-infected permissive and nonpermissive cells, and their phosphorylation patterns were compared. No evidence was found for a different phosphorylation pattern of T antigens in transformed cells. (Author abstract) (62 Refs)

48. A CELLULAR PROTEIN PHOSPHORYLATED BY THE AVIAN SARCOMA VIRUS TRANSFORMING GENE PRODUCT.

Erikson E, Erikson RL
Health Sciences Center, Univ. Colorado, 4200 E. Ninth Ave., Denver, CO, 80262
Haematol Blood Transfus; 26:397-401 1981

Experiments are described which demonstrate that a newly phosphorylated protein in avian sarcoma virus (ASV)-transformed chicken cells with a mol wt of approx 34,000 (34K) and an isoelectric focusing of about 7.5 is a src-specific substrate found in normal cells and that upon transformation it is phosphorylated in ASV-infected cells of both avian and mammalian origin. This protein appears to be a substrate for the phosphotransferase activity associated with pp60src. This protein, or an analogous protein was partially phosphorylated in all ASV-transformed cells examined to date. The pp60src-specific nature of the phosphorylation is shown by the phosphorylation of 34K by pp60src in vitro at a site identical to that phosphorylated in vitro at a site identical to that phosphorylated in transformed cells. This result strongly suggests that 34K is a direct rather than indirect substrate of pp60src in the cell. This result also suggests that pp60src acts as a protein kinase in the transformed cell as well as in vitro and that it mediates transformation, at least in part, by phosphorylation of 34K and perhaps of other normal cell proteins. This conclusion does not eliminate the possibility that pp60src may have other functions that influence transformation. (11 Refs)

49. COMPARISON OF PHOSPHORYLATION OF TWO POLYOMA VIRUS MIDDLE T ANTIGENS IN VIVO AND IN VITRO.

Schaffhausen B, Benjamin TL
Dept. Pathology, Harvard Medical Sch., Boston, MA, 02115
J Virol; 40(1):184-196 1981

Two species of polyoma virus middle T antigen were detected in both lytically infected and transformed cells by in vitro kinase assay of immunoprecipitates. A minor species with an apparent mol wt of 58,000 (58K) represented less than 10% of the total middle T protein. This species was roughly 10x more active as a phosphate acceptor than was the predominant 56K form. Partial proteolytic mapping experiments showed that the same site was phosphorylated in both species. Mapping of the middle T antigens from a series of deletion mutants suggested that the major site of phosphorylation is tyrosine residue 315. Phosphorylation occurred on both middle T species in vivo, involving sites predominantly other than the tyrosine labeled in vitro. The 56K and 58K middle T forms differed from each other in their in vivo phosphorylation patterns. Some phosphate was incorporated into the 58K species in a region of the molecule to which at least part of the apparent mol wt difference could be mapped. hr-t mutant NG-59, which codes for a slightly altered middle T, produced only a single species (56K) which was inactive in the in vitro kinase reaction. Moreover, no 58K species appeared in vivo with this mutant.The hr-t mutants are therefore defective in both aspects of phosphorylation. Phenotypically normal revertant cells of a polyoma transformed line failed to express any middle T antigens or associated kinase activity. (Author abstract) (43 Refs)

50. COMPARISON OF CAMP-DEPENDENT PROTEIN KINASE IN NORMAL AND ROUS SARCOMA VIRUS TRANSFORMED CHICK EMBRYO FIBROBLASTS.

Kudlow JE, Watson RK, Gill GN
Dept. Medicine, Div. Endocrinology, Univ. California, San Diego, Sch. Medicine, La Jolla, Ca, 92093
J Cyclic Nucleotide Res; 7(3):151-159 1981

Chicken embryo fibroblasts (CEF) were transformed with Schmidt-Ruppin Subgroup D Rous sarcoma virus (RSV). The activity of cyclic AMP (cAMP) dependent protein kinase (A kinase) in transformed cells was compared with th in normal cells. Two A kinase regulatory subunits from chicken skeletal muscle, both specific for cAMP, were characterized by photoaffinity labeling. Mol wt of the units were 45,000 and 42,000 Mr, about 4-5,000 daltons smaller than corresponding mammalian subunits. A single isoenzyme corresponding to the smaller subunit was found in equal quantities in normal and transformed CEF. Total cAMP binding and total A kinase activity were the same in normal and transformed CEF. The apparent Km for activation of A kinase by cAMP was 35 nanoM for each. Apparently RSV does not directly affect the amount or activity of cAMP-dependent A kinase. (31 Refs)

51. MECHANISMS OF KIRSTEN MURINE SARCOMA VIRUS TRANSFORMATION-INDUCED CHANGES IN THE COLLAGEN PHENOTYPE AND SYNTHETIC RATE OF BALB 3T3 CELLS.

Bateman JF, Peterkofsky B
(c/o Peterkofsky) Lab. Biochemistry, Div. Cancer Biology and Diagnosis, NCI, NIH, Bethesda, MD, 20205
Proc Natl Acad Sci USA; 78(10):6028-6032 1981

Specific viral transformation rather than cell selection can explain the previously observed increase in the proportion of Type III procollagen compared to Type I procollagen in BALB 3T3 cells transformed by Kirsten murine sarcoma virus (Ki-MSV). Two subclones of BALB 3T3 A31 were productively infected with a temperature-sensitive Ki-MSV in the presence of helper murine leukemia virus (MLV), resulting in virtually complete transformation of cultures and eliminating selection of transformed foci. Analysis of radioactive collagen, derived from procollagen by pepsin treatment, showed that both of the tsKi-MSV/MLV-transformed subclones contained a four-fold greater proportion of Type III procollagen than did control MLV-infected cultures. A nonproducer derivative exhibited an even greater change (10-fold), indicating that viral replication was irrelevant. After 48 hr at a nonpermissive temperature, tsKi-MSV-transformed cells retained a high proportion of Type III procollagen, suggesting that either this change is not induced by src protein or else there is a slowly reversible or irreversible step involved. Alternatively, Type III procollagen mRNA may be long lived. In contrast, the relative rate of procollagen synthesis in transformed cells was clearly regulated by src protein. Translation of mRNA from cells preincubated at permissive or nonpermissive temperatures revealed that the decreased relative rate can be explained by a simultaneous small decrease in the level of procollagen mRNA and a large increase in mRNA for noncollagen proteins. (Author abstract) (36 Refs)

52. TROPOMYOSIN IS DECREASED IN TRANSFORMED CELLS.

Hendricks M, Weintraub H
Hutchinson Cancer Center, 1124 Columbia St., Seattle, WA, 98104
Proc Natl Acad Sci USA; 78(9,part2):5633-5637 1981

The steady-state level and synthesis of a pair of polypeptides of Mr 33,000 and 35,000 in chicken embryo fibroblasts (CEF) transformed by Rous sarcoma virus (RSV) are significantly decreased relative to normal CEF; however, the decrease is more pronounced in the case of the Mr 35,000 polypeptide. These polypeptides have been identified as the alpha and beta subunits of CEF tropomyosin by selective staining with tropomyosin antibody, two-dimensional gel electrophoresis, partial peptide analysis, and solubility properties. The decrease in tropomyosin is shown to be a transformation-specific phenomenon in that it does not occur after infection with a virus deleted in src sequences. Decreased synthesis of tropomyosin is also observed in quail cells transformed by MC29 (a retrovirus with a different onc gene than that in RSV) and also in chemically transformed quail cells. The decrease in tropomyosin is probably not a direct result of the disruption of the microfilament system in transformed cells because disruption of the microfilament system with trypsin or cytochalasin B in normal CEF does not lead to a decrease in tropomyosin synthesis. A decrease in tropomyosin in CEF after transformation may be a result of a pleiotropic effect that results in the transcriptional inactivation not only of the tropomyosin gene but also of the fibronectin and procollagen genes described by others. (Author abstract) (34 Refs)

53. AN INCREASE IN CALMODULIN DURING GROWTH OF NORMAL AND CANCEROUS LIVER IN VIVO.

MacManus JP, Braceland BM, Rixon RH, Whitfield JF, Morris HP
Animal/Cell Physiology Group, Natl. Res. Council Canada, Ottawa K1A OR6, Canada
FEBS Lett; 133(1):99-102 1981

Change in the calcium receptor protein, calmodulin (CaM), during growth of normal liver and a greater content of CaM in solid liver tumors is reported. Specific pathogen free liver as well as Morris hepatomas were utilized. Tissues were excised, homogenized and total, soluble, and particulate samples prepared. Radioimmunoassay for CaM was performed using 125I labeled CaM, 2 ug anti-CaM, and standard amounts of CaM or tissue extracts. CaM content was also measured by stimulation of a cyclic-nucleotide phosphodiesterase (PDE). Results show no change in CaM content of liver after sham hepatectomy. CaM content in the soluble fraction of liver increased three fold after 68% partial hepatectomy, returning to normal after 18 hr. No change was observed in the particulate fraction of regenerating liver. Assay of CaM dependent cyclic nucleotide PDE confirmed increase of CaM during liver regeneration. The increase of CaM during liver regeneration coincides with the time when calcium is required for DNA synthesis. The relevance of the CaM rise to the calcium dependence has yet to be established. Fetal or neonatal liver had the same CaM concentration as adult liver. Various liver tumors contained more CaM than normal adult or fetal liver. The increase in CaM content in virally transformed cells in vitro is apparently a characteristic of the neoplastic state. The evidence of CaM increase during regeneration possibly indicates that CaM may be involved with the control of cell proliferation. (23 Refs)

54. DNA METHYLATION AND METHYLASE LEVELS IN NORMAL AND MALIGNANT MOUSE HEPATIC TISSUES.

Lapeyre JN, Walker MS, Becker FF
Dept. Pathology, Section Experimental Pathology, M.D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Carcinogenesis; 2(9):873-878 1981

DNA methylation levels (expressed as the percentage of 5-methylcytosine relative to total cytosines) were measured in normal mouse liver, primary hepatocellular carcinomas (PHCs) in male C3H mice, PHCs induced in male C7Bl/6N mice by chlordane, N-acetylaminofluorene, or 3'methyl-4-dimethylaminoazobenzene, and spontaneous and chemically induced PHCs in male (C7BL/6H x C3H/HeN)F1 (B6C3) mice. All tumors demonstrated an undermethylation of their genomes, compared with normal livers of age-matched controls. The undermethylation was not due to inactivation of or deficiency in DNA methylase activity, since enzyme levels in tumor nuclei were higher than background levels. The possibility that aberrations in DNA methylation are involved in the transformation of normal differentiated cells to neoplastic cells is discussed. (57 Refs)

55. LDHK, A UNIQUELY REGULATED CRYPTIC LACTATE DEHYDROGENASE ASSOCIATED WITH TRANSFORMATION BY THE KIRSTEN SARCOMA VIRUS.

Anderson GR, Kovacik WP, Marotti KR
Dept. Cell and Tumor Biology, Roswell Park Memorial Inst., Buffalo, NY, 14263
J Biol Chem; 256(20):10583-10591 1981

A novel isozyme of lactate dehydrogenase is detected in various cells transformed by the Kirsten murine sarcoma virus (KiMSV). This isozyme, designated LDHk, is strongly inhibited by physiological concentrations of oxyen, in an apparently cooperative fashion. LDHk is inhibited by guanosine triphosphate and related compounds, in an noncompetitive fashion. LDHk is found with both 35,000-and 22,000-dalton subunits, although these probably cleave from a 57,000-dalton precursor. In studies utilizing a temperature-sensitive transforming gene mutant of the Kirsten sarcoma virus, we find in vivo expression of LDHk is also temperature-sensitive. In studies using either crude cell-free extracts or purified LDHk, we find the enzyme from cells infected with a temperature-sensitive transforming gene mutant of KiMSV is thermolabile relative to that from wild type KiMSV-infected cells. (Author abstract) (34 Refs)

CELL SURFACE PHENOMENA OF TRANSFORMATION

56. LY 11.2: A CELL SURFACE ANTIGEN THAT MAY IDENTIFY MURINE LYMPHOCYTES SUSCEPTIBLE TO TRANSFORMATION BY ONCOGENIC AGENTS.

Meruelo D, Paolino A, Flieger N, Offer M, Dworkin J
Irvington House Inst., Dept. Pathology, New York Univ. Medical Center, New York, NY, 10016
Fed Proc; 40(12):2717-2720 1981

Ly 11.2, a newly defined T cell surface antigen, is present on two lymphocyte subpopulations playing a key role during leukemogenesis: the natural killer cell and possibly the target cells for malignant transformation by oncogenic agents. Antibodies to this cell surface marker should greatly help in the study, isolation, and characterization of these cells. (Author abstract) (20 Refs)

57. IGG-FC-BINDING RECEPTORS IN CELLS ABORTIVELY INFECTED, OR TRANSFORMED, BY HUMAN CYTOMEGALOVIRUS.

Gonczol E, Boldogh I, Vaczi L
Inst. Microbiology, Univ. Medical Sch., P. O. B. 17, H-4012 Debreen, Hungary
Acta Microbiol Acad Sci Hung; 28(2):157-164 1981

IgG-Fc-binding membrane and cytoplasmic receptors were investigated in human embryonic fibroblast and hamster embryonic fibroblast cultures prepared, respectively, from human abortion material and Syrian golden hamster embryos, and also in cells transformed by human cytomegalovirus (HCMV). Cytoplasmic receptors were formed in abortively infected cells and similar receptors were formed on the cell surface of a low proportion (12-15%) of the cells infected either productively (human cells) or abortively (hamster cells). In the presence of cytosine arabinoside hydrochloride (ara-C), the receptors were formed in both the cytoplasm and cell membrane more readily than without ara-C. Cytoplasmic IgG-Fc receptors had formed in a very low proportion (2%) of the human cells and in a much higher proportion (65%) of the hamster cells while DNA synthesis was inhibited. IgG-Fc-binding receptors were transiently present in the cytoplasm and on the surface of cells being abortively infected by HCMV. The receptors were also present in cells transformed in vitro by HCMV (87-TRH-5 and CX-90-3B), as well as in cells of lines TSC-1 and TSC-2 from tumors induced by these cells. Thus, the indirect immunofluorescence test performed with sera containing no HCMV antibodies may give a positive reaction in the cytoplasm and/or cell membrane of the transformed cells. (18 Refs)

58. PERICELLULAR MATRIX OF VIRUS-TRANSFORMED MOUSE EPITHELIAL CELLS (MEETING ABSTRACT).

Keski-Oja J
Department of Virology, University of Helsinki, SF-00290 Helsinki 29, Finland
Eighth European Congress of Pathology, August 30-September 4, 1981, Helsinki, Finland. The Congress 92 pp., 1981.

Mouse embryo epithelial cells, MMC-E were transformed with Moloney murine sarcoma virus (MSV) or with ecotropic murine leukemia virus (C3H/MuLV). Transformed cell colonies, isolated using soft agar techniques were analyzed for their production of connective tissue glycoproteins. The nontransformed, MSV-transformed and MuLV-transformed cells produced fibronectin, laminin, type I collagen and small amounts of type III collagen as shown by immunofluorescence analysis of their pericellular matrices. The MuLV- and MSV- transformed cells produced enhanced amounts of fibronectin into their growth media as shown by metabolic labeling and polypeptide analysis. Nontransformed MMC-E cells mainly produced type I procollagen. A significant increase in the glycoprotein production was seen by the MuLV-transformed cells, whereas small changes in the collagen production were apparent after MSV-transformation. MuLV-transformed cells produced enhanced amounts of type I collagen and also some type IV collagen. The ratio of the procollagen type I chains in the matrix was significantly altered in the transformed cells indicating that type I procollagen is mainly deposited in their pericellular matrix as alpha 1 (I)-trimer. Unlike virus-transformed fibroblastic cells these transformed epithelial cells deposited and retained connective tissue glycoproteins in their matrices. The ability of virus-transformed epithelial cells to retain pericellular matrices is a major difference between them and virus-transformed fibroblastic cells in culture. (1 Ref)

59. BIOCHEMICAL CHARACTERIZATION OF AN ANTIGEN ASSOCIATED WITH ACUTE LYMPHOBLASTIC LEUKEMIA AND LYMPHOCYTE PRECURSORS.

Newman RA, Sutherland DR, Greaves MF
Imperial Cancer Res. Fund Lab., P.O. Box 123, Lincoln's Inn Field, London WC2A 3 PX, England
Haematol Blood Transfus; 26:326-328 1981

An antigen (ALLA) occurring on the surface membrane of cells from patients with common acute lymphoblastic leukemia (ALL) was previously identified. ALLA was also found in some cases of undifferentiated leukemias and chronic myeloid leukemia and in a small proportion of normal bone marrow cells. ALLA from the cell line Nalm-1 was characterized biochemically. ALLA is a glycosylated polypeptide of approx 100,000 daltons. No intrachain disulfide linkages are present. ALLA shows 50% binding with lentil lectin, but 100% binding with Ricinis communis lectin. Lectin binding and nonbinding forms form identical homogeneous spots in two-dimensional isoelectric focusing with a pI of 5.1-5.5. Neuraminidase treatment of both forms causes a shift of approx 0.6 towards the basic end of the gel. Treatment with tunicamycin and glycosidases indicate that up to 25% of ALLA mol wt may be carbohydrate, but carbohydrate is not involved in the antigenic site. ALLA is apparently not integral to the cell membrane, but is closely associated with it. Presence of ALLA in some normal bone marrow cells suggests the antigen is a normal product reflecting target cells for malignant transformation and/or the stage of maturation arrest of ALL cells. (11 Refs)

MORPHOLOGICAL AND OTHER BIOLOGICAL ASPECTS OF ONCOGENIC TRANSFORMATION

60. COLONY FORMATION IN AGAROSE GELS CONTAINING 2-DEOXYGLUCOSE: ITS RELATIONSHIP WITH MALIGNANT TRANSFORMATION.

Gavilondo JC, Perez RR, Lage AD
Inst. Oncology and Radiobiology, MINSAP 29 y F., Habana 4, Cuba
Neoplasma; 28(3):291-299 1981

At the light of the increasing evidence that malignant transformation is a multistep process the wide correlation between growth in soft agar and various degrees of tumorigenicity suggests that this could be a property of the early stages of malignant transformation. In the present paper we give evidence indicating that colony formation in agarose gels containing deoxyglucose can operate as a more restrictive criterion than growth in soft agar for malignant transformation in vitro, possibly associated to advanced stages in this process. (Author abstract) (19 Refs)

61. CHARACTERIZATION OF HUMAN CELLS TRANSFORMED BY CHEMICAL AND PHYSICAL CARCINOGENS IN VITRO.

Milo GE, Oldham JW, Zimmerman R, Hatch GG, Weisbrode SA
Dept. Physiological chemistry, Coll. Medicine, Ohio State Univ., 333 W. 10th Ave., Columbus, OH, 43210
In Vitro; 17(8):719-729 1981

Several different classes of chemical carcinogens induced the transformation of human fibroblasts grown in vitro. Characteristics of the events that occur from time of treatment through the expression of neoplastic transformation are presented. The S-phase appeared to be the portion of the cell cycle most vulnerable to insult. Staging of the cells by blocking them in G1 before releasing them to proceed through scheduled DNA synthesis (S) was required to induce reproducible transformation. Compounds such as insulin were added to the cells upon release from the block to sensitize the cells to the carcinogen that was added during S. Growth of the transformed cells as distinct from nontransformed cells was promoted by growth in medium supplemented with 8X nonessential amino acids. Carcinogen-treated cells in the early stage of transformation exhibited abnormal colony morphology and were able to grow at 41 C, in air atmosphere, and in medium supplemented with only 1% serum. In addition, the transformed cells were insensitive to KB cell lysate and exhibited density independent, as well as anchorage independent, growth (ie, growth in 0.33% agar). Cells that grew in soft agar also produced undifferentiated mesenchymal tumors in preirradiated nude mice. (Author abstract) (19 Refs)

62. SEQUENCE OF EVENTS IN THE TRANSFORMATION PROCESS IN CELLS INFECTED WITH A TEMPERATURE-SENSITIVE TRANSFORMATION MUTANT OF MOLONEY MURINE SARCOMA VIRUS.

Brown RL, Horn JP, Wible L, Arlinghaus RB, Brinkley BR
(c/o Arlinghaus) Dept. Tumor Virology, Univ. Texas System Cancer Center, M. D. Anderson Hosp. Tumor Inst., Houston, TX, 77030
Proc Natl Acad Sci USA; 78(9,part2):5593-5597 1981

Normal rat kidney cells infected with the temperature-sensitive transformation mutant of Moloney murine sarcoma virus were used to study the biochemical and morphological changes that occur during transformation. The infected cells exhibited a normal morphology at the nonpermissive temperature (39 C) and a transformed morphology at the permissive temperature (33 C). A new viral protein was detected 2 hr after shift to the permissive temperature as a polyprotein with an estimated Mr of 85,000 (p85). Scanning electron microscopy of the cells within 5 hr after shifting them to the permissive temperature showed that they became smaller and rounded with numerous elongated microvilli. In an earlier study, changes in hexose uptake were found to occur 8-12 hr after the shift. By 48 hr, the cells had the morphology of a fully transformed cell. Concomitant with the changes in the morphology were alterations in the cytoplasmic microtubule complex. At the nonpermissive temperature, the complex consisted of a lacy network of microtubules. Within 5 hr at the permissive temperature, the lacy network was still present but the microtubules were more diffusely stained and less discernible. By 48 hr, the microtubules were so diffuse that the lacy network could not be recognized. Alterations in the F-actin cables did not occur until 24 hr after shifting the cells to the permissive temperature. Enucleation of the cells at the nonpermissive temperature and shifting the cytoplasts to the permissive temperature did not result in the synthesis of detectable p85 or in any alteration of the cytoplast morphology or microtubule complex, suggesting that the temperature-sensitive lesion affects some event occurring in the nucleus. (Author abstract) (28 Refs)

ASSAYS OF ONCOGENIC TRANSFORMATION

63. IN VITRO MODELS AND METHODS FOR BIOASSAY AND STUDIES OF CELLULAR MECHANISMS.

Belman S, Casto B, Flessel CP, Lane BP, Loeb L, Rossman T, Sirover MA, Vainio H, Whiting R, Zakour R

New York Univ. Medical Center, New York, NY, 10016

Environ Health Perspect; 40:35-42 1981

The use of in vitro systems to detect metal carcinogens and study the mechanisms of carcinogenesis is discussed. These systems include mutagenesis in bacterial and mammalian cells, in vitro transformation, cell-free systems, chromosome aberrations, sister chromatid exchanges, and micronucleus tests. Chromium carcinogenesis is described as an example. General conclusions and recommendations for the future are presented. (56 Refs)

64. CHEMICAL-VIRAL CO-CARCINOGENESIS IN VITRO USING CLONED MAMMARY EPITHELIAL CELLS AND MOUSE MAMMARY TUMOR VIRUS (MEETING ABSTRACT).

Howard DK, Fisher PB, Schlom J

National Cancer Institute, National Institutes of Health, Bethesda, MD, 20205

In Vitro; 17(3):236 1981

We have evaluated the effect of mouse mammary tumor virus (MMTV) and 7,12-dimethylbenz(a)anthracene (DMBA), either alone or in combination, on mammary epithelial cells in vitro. A single-cell clone (clone 2), was derived from the normal mouse mammary gland cell line, C57MG, and was shown to be of murine origin by karyotyping, isoenzyme analyses, and by immunofluorescence using species-specific antisera. This clone failed to induce tumors in syngeneic or athymic (nude) mice. The epithelial origin of the cells was demonstrated by the presence of desmosomes, tonofibrils and secretory granules. Clone 2 cells were infected with MMTV host-range variant MMTV (RIII) vp4, and both infected and mock-infected cultures were treated with DMBA. Cultures treated with both virus and carcinogen exhibited morphological changes and a slight increase in ability to grow in soft agar after 5 to 7 subcultures. The most striking alteration in the phenotype of cells exposed to the combination of MMTV and DMBA, however, was an increase in their tumorigenic potential in athymic mice. Cultures treated with virus alone or DMBA alone did not show an increase in tumorigenicity. This cell-culture model system now permits the study of the interaction of chemicals and MMTV in the initiation and promotion of mammary cell transformation. (no Refs)

GENERAL REVIEWS AND OTHER RELATED STUDIES

65. THE RELATIVE ROLE OF VIRAL TRANSFORMATION AND SPECIFIC CYTOGENETIC CHANGES IN THE DEVELOPMENT OF MURINE AND HUMAN LYMPHOMAS.

Klein G
Dept. Tumor Biology, Karolinska Institutet, 104 Stockholm 60, Sweden
Haematol Blood Transfus; 26:3-10 1981

Lymphoma and leukemia development in mice and men, where there is extensive evidence for the role of the specific genetic changes recognizable at the chromosome level, is discussed. Topics considered include human lymphomas, murine T cell leukemia, the relationship of trisomy to murine T-cell leukemia, and the role Abelson virus as a transducer or cellular gene. Various conclusion were drawn: transformation in vitro is not synonymous with tumorigenicity in vivo; host cell controls can modify the expression of transformation in vivo; and host cell controls can reverse tumorigenic to nontumorigenic phenotypes. The concept of convergence is discussed in relation to tumor evolution. According to this concept viruses play essentially the role of initiators in tumor progression, specific genetic changes are responsible for the transition of preneoplastic to frankly malignant cells, and the cytogenetic changes act by shifting the balance between genes that favor progressive growth in vivo and genes that counteract it. (85 Refs)

66. SOMATIC MUTATION/NEODIFFERENTIATION/ SELECTION AND THE ORIGINS OF HUMAN CANCERS.

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Dept. Veterinary Science, Coll. Agriculture and Life Sciences, Univ. Wisconsin, 1655 Linden Drive, Madison, WI, 53706
Med Hypotheses; 7(9):1157-1168 1981

The etiology of cancer is considered in terms of underlying biological mechanisms: somatic mutation (an alteration in genomic information content) or defective differentiation (alteration in genomic information expression). Human carcinogens, including radiation, chemicals, and viruses or viral components, are discussed. Chemicals have been shown to be responsible for virtually all epithelial cancers. Considering human carcinogenesis to be a multistep procedure, it is possible to accept both hypotheses for the origin of cancer. According to the blocked ontogeny hypothesis of cancer, it is suggested that an agent capable of blocking natural differentiation might bring about a partial or total blockage of natural restraints on proliferation produced by differentiated cells. This theory is discussed in relation to hemoglobinopathies and thalassemias, caused by inherited mutations and genetic deletions that affect the development of Hb production. Others have suggested that most human cancers are not caused by local genomic mutation but are more likely the result of genetic transpositions or rearrangements. It is unknown whether or not or to what extent natural cellular differentiation is mediated by transpositions involving moveable genetic elements. The authors concluded that both genetic transposition and 'autocrine secretion' are within the confines of and consistent with the more general blocked ontogeny hypothesis, and together help provide a plausible mechanism for a somatic mutation/neodifferentiation/ selection theory of human cancer. (51 Refs)

67. HISTORY OF CANCER INVESTIGATION.

Gomez P, Rosado A
Unidad de Investigacion Clinica, Centro Medico Nacional, IMSS, Av. Cuauhtemoc 330, Mexico 7, D.F., Mexico
Arch Invest Med (Mex); 12(3):361-375 1981

Important biological hypotheses of carcinogenesis are reviewed: the majority are concerned with alterations in cellular genetic material. Chemical, physical, and viral carcinogens and their actions on cell metabolism are presented. Carcinogenesis occurs through somatic mutation resulting from external and internal factors. Solving the cancer riddle depends on advances in molecular biology and genetics with respect to regulatory mechanisms of cell differentiation and genetic control of differentiated cells. (49 Refs)

68. MECHANISMS OF TOLERANCE TO DNA LESIONS IN MAMMALIAN CELLS.

Meneghini R, Menck CF, Schumacher RI
Dept. Biochemistry, Inst. Chemistry, Univ. Sao Paulo, C.P. 20780, Sao Paulo, Brazil
Q Rev Biophys; 14(3):381-432 1981

The way in which mammalian cells deal with a large burden of unexcised DNA lesions is discussed. The biological consequences of unexcised DNA lesions are considered in terms of cell killing, cell mutation, cell transformation, enhanced virus reactivation, and sister chromatid exchanges. These different biological effects seem to be triggered during DNA replication. Thus, the damaged template has to be replicated in order for the chain of events leading to a certain effect to be initiated. DNA replication on a damaged template is discussed in relation to information from bacterial systems, DNA containing lesions replicated in mammalian cells, effect of template-strand lesions on the rate of DNA synthesis and the structure of the daughter strand, inhibition of replication fork by lesions in the template strand, DNA synthesis along the lesions (postreplication repair), and mechanisms of postreplication repair (recombination, branch migration, 'translesion synthesis', and relief of blocked sites by joining of adjacent replicons). Hints of the inducibility of tolerance to DNA lesions come from distinct approaches such as the enhancement of DNA chain elongation, recovery of the rate of DNA synthesis, recovery in survival, enhanced virus reactivation, and induction of proteins by DNA-damaging agents. (163 Refs)

69. EXPRESSION OF VIRAL GENES IN TRANSFORMED CELLS.

Ratovitskii EA
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Usp Sovrem Biol; 92(1):3-18 1981

Experimental data on the expression and integration of viral genes in the permissive and nonpermissive cells and on the role of viral genes in transformation of target cells are reviewed. Numerous in vitro and in vivo studies showed that the genome of host cells can control an expression of oncornavirus genes at transcription, transport of messenger RNA from the nucleus into cytoplasm, and translation stages. Viral genes were shown to stimulate globin synthesis and to inhibit collagen synthesis in chick fibroblasts transformed with Rous sarcoma virus. It was emphasized that further research would clarify whether the product of src gene affects directly expression of cellular genes or whether the exogenous provirus sequences only initiate the endogenous 'cancer' genes. (202 Refs) (In RUS)

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1. CHEMICAL COMPOUNDS AND CANCER RISK.

Schramm T, Janisch W
Zentralinstitut fur Krebsforschung der Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin, E. Germany
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Inst. Occupational Health, Gydas vei 8, Oslo 3, Norway
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Kazantzis G
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Dept. Chemistry, Univ. Maryland Baltimore County, Catonsville, MD, 21228
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Universitatsklinik fur Innere Medizin 'Theodor Brugsch', Bereich Medizin der Humboldt-Universitat, Schumannstrasse 20/21, DDR-1040 Berlin, E. Germany
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Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139
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(c/o P. Lohman), Medical Biological Lab. TNO., P.O. Box 45, 2280 AA Rijswijk, The Netherlands
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Jennette KW
Dept. Chemistry, Dartmouth Coll., Hanover, NH, 03755
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Becker FF
M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
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Environ Health Perspect; 40:197-205 1981

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Vainio H, Sorsa M
Dept. Industrial Hygiene and Toxicology, Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Environ Health Perspect; 40:173-180 1981

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26. METAL INTERACTIONS IN CARCINOGENESIS: ENHANCEMENT, INHIBITION.

Nordberg GF, Andersen O
Dept. Environmental Hygiene, Umea Univ., Umea, Sweden
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Rossman TG
Inst. Environmental Medicine, New York Univ. Sch. Medicine, 550 First Ave., New York, NY, 10016
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Harvard Medical Sch., Boston, MA, 02115
Mutat Res; 87(1):17-62 1981

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Sirover MA
Dept. Pharmacology, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Environ Health Perspect; 40:163-172 1981

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TRANSFORMATION GENE STRUCTURE

1. THE V-SIS TRANSFORMING GENE OF SIMIAN SARCOMA VIRUS IS A NEW ONC GENE OF PRIMATE ORIGIN.

Wong-Staal F, Dalla Favera R, Gelmann EP, Manzari V, Szala S, Josephs SF, Gallo RC
Lab. Tumor Biology, NCI, Bethesda, MD, 20205
Nature; 294(5838):273-275 1981

Studies on the cloned simian sarcoma virus (SSV) genome are presented which show that a 1.2-kilobase transformation-specific viral onc gene, v-sis, is distinct from other genes and is derived from a woolly monkey which had previously co-habited with a gibbon before it developed sarcoma. A PstI-PstI fragment of the SSV genome that contains approx 250 base pairs (bp) of 5' v-sis sequences and 900 bp of nondefective helper virus (SSAV)-derived sequences were subcloned into the bacteriophage M13. The single-stranded phage DNA was then partially digested with DNase and terminally labeled with 32P. Labeled DNA was hybridized to cellular DNA from tissues of different animals and resultant hybrids were assayed by their resistance to S1 nuclease. Primate DNA hybridized significantly better than DNA from non-primates. Among primates, highest homology was obtained with woolly monkey DNA. The SSAV genome had no detectable homology to primate DNA and its distant homology to rodent DNA could only be monitored by non-stringent hybridization conditions. It is concluded that v-sis originated from woolly monkey DNA. The close relatedness of SSAV to different gibbon ape leukemia virus isolates and the revelation that the woolly monkey that yielded SSV/SSAV co-habited with a gibbon before it developed sarcoma suggests that SSAV was transmitted from gibbon to woolly monkey during that period, and that in a single infection event, SSAV had recovered an onc gene from woolly monkey to generate SSV. To date this is the only onc gene of primate origin. (24 Refs)

2. VERTEBRATE DNAS CONTAIN NUCLEOTIDE SEQUENCES RELATED TO THE TRANSFORMING GENE OF AVIAN MYELOBLASTOSIS VIRUS.

Bergmann DG, Souza LM, Baluda MA
Univ. California Los Angeles Sch. Medicine, Los Angeles, CA, 90024
J Virol; 40(2):450-455 1981

Avian myeloblastosis virus contains a continuous sequence of approx 1,000 nucleotides which may represent a gene (amv) responsible for acute myeloblastic leukemia in chickens. This sequence appears to have been acquired from chicken DNA and to be substituted for the envelope gene in the viral genome. We used hybridization probes enriched for the amv sequences and conditions that facilitate annealing of partially homologous nucleotide sequences to show that cellular sequences related to amv are present in the genomes of all vertebrates ranging from amphibians to humans but were not detected in fish, sea urchins, or Escherichia coli. In contrast to the preceding findings, nontransforming endogenous proviral nucleotide sequences closely related to the remainder of the avian myeloblastosis virus genome and to the entire myeloblastosis-associated helper virus are present only in chicken DNA. The amv-related cellular sequences appear to be highly conserved during evolution and to be contained at only one or a few locations in the genome of vertebrates. Within closely related species, they appear to share common evolutionary genetic loci. These findings and similar ones obtained with other highly oncogenic retroviruses containing a tran sforming gene suggest a general mechanism for acquisition of viral oncogenic sequences and an essential role for these sequences in the normal cellular state. (Author abstract) (29 Refs)

3. INTEGRATION OF ROUS SARCOMA VIRUS DNA INTO CHICKEN EMBRYO FIBROBLASTS: NO PREFERRED PROVIRAL ACCEPTOR SITE IN THE DNA OF CLONES OF SINGLY INFECTED TRANSFORMED CHICKEN CELLS.

Lerner TL, Skalka AM, Hanafusa H
Rockefeller Univ., New York, NY, 10021
J Virol; 40(2):421-430 1981

We analyzed retroviral integration into a host genome by using avian sarcoma virus infection of natural target cells under conditions where secondary integration via virus spread was inhibited. This was accomplished by using the noninfectious pol-env-alpha variant of the Bryan high-titer strain of Rous sarcoma virus. A total of 12 independent Bryan high-titer Rous sarcoma virus-transformed chicken embryo fibroblast clones were obtained and mapped by using restriction endonucleases. Provirus-cell junction fragments were identified with appropriate hybridization probes. We found that expression of the viral genes could occur after proviral integration at many sites on the chicken genome and that there was no apparent preference for specific integration sites. (Author abstract) (48 Refs)

4. RESTRICTION OF REPLICATION OF ROUS SARCOMA VIRUS MEDIATED BY THE SRC REGION OF THE GENOME: ANALYSIS OF THE FORMATION AND INTEGRATION OF VIRAL DNA AND THE EFFECTS OF CONDITIONAL AND NONCONDITIONAL MUTATIONS IN SRC.

Neiman PE, Stone J, Gilbert L, Fincham VJ, McMillin-Helsel C, Wyke JA
Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
Virology; 114(2):516-525 1981

The growth of most Rous sarcoma viruses (RSV) is severely restricted on MSB-1 cells (a line of chicken T lymphoblasts) in comparison to growth on chicken embryo fibroblasts (CEF). Nonconditional transformation defective mutants of RSV from which the complete src region has been deleted (td RSV) are not subject to growth restriction. We examined the formation and integration of RSV and td RSV in MSB-1 cells following high multiplicity infection. Nearly equivalent quantities of the linear form of unintegrated RSV and td RSV DNA were formed in these cells during the first 10 hr after infection. Linear RSV DNA from MSB-1 cells could not be distinguished from linear RSV from CEF by restriction endonuclease analysis and by previously described transfection assays. Beyond 10 hr after infection, and with progressive cell growth in the MSB-1 cultures, the level of RSV linear DNA rapidly decreased. Presumptive circular RSV DNA was detected only transiently, and at very low levels, about 15 hr after infection. Association of RSV DNA with high-mol wt chromosomal DNA, ie, integration, was not detected in this study. In contrast, nearly constant levels of td RSV unintegrated linear DNA and, after 20 hr, circular DNA persisted in MSB-1 cells for at least 7 days after infection. Integration of td RSV proviral DNA was inefficient, occurring in only about 5% of MSB-1 cells (even at very high multiplicities of infection) in the first round of infection, and in 25-40% of cells by 3 days after infection. Almost all MSB-1 cells contained td RSV DNA produced virus. Analysis of eight nonconditional transformation defective mutants of RSV which retain the src region to different extents showed that all of these mutants replicated to the same normal titer on MSB-1 cells as on CEF without further deletion of the src region. Two temperature sensitive src mutants of RSV showed similar growth restriction on MSB-1 cells at both 35 C and 41 C, indicating that thermal inactivation of the src gene product could not abrogate the replication block. These studies clearly demonstrate that the presence of the src region in RSV impedes the formation and/or integration of provirus in some types of host cells. (Author abstract) (24 Refs)

5. MOLECULAR CLONING OF EQUINE HERPESVIRUS TYPE 1 DNA: ANALYSIS OF STANDARD AND DEFECTIVE VIRAL GENOMES AND VIRAL SEQUENCES IN ONCOGENICALLY TRANSFORMED CELLS.

Robinson RA, Tucker PW, Dauenhauer SA, O'Callaghan DJ
Dept. Microbiology, Univ. Mississippi Medical Center, Jackson, MS, 39216
Proc Natl Acad Sci USA; 78(11,part2):6684-6688 1981

Genomic DNA sequences of equine herpesvirus type 1 (EHV-1) have been cloned as BamHI and EcoRI restriction fragments into the plasmid pBR322 and propagated in Escherichia coli. With the exception of two EcoRI restriction fragments that reside in the S region of the viral genome, all of the cloned fragments demonstrated the same electrophoretic mobilities, restriction cleavage sites, and blot-hybridization patterns as did the parent fragments produced by BamHI or EcoRI digestion of virion DNA. The EcoRI J fragment and the BamHI E fragment of the L-region terminus were cloned after the addition of appropriate linker oligonucleotides. Fragments originating from each of the two isomeric forms of EHV-1 DNA were contained in this library of clones. Supramolar DNA fragments present only in the DNA of defective interfering (DI) particles of EHV-1 were generated from Bgl II digestion of DNA preparations enriched for EHV-1 DI particles and were cloned as Bgl II and EcoRI fragments into the plasmid vector. The cloned viral sequences represented in this defective genome mapped to the S region of EHV-1 DNA. Blot-hybridization analysis of EHV-1 transformed and tumor cell DNAs with the cloned BamHI B fragment confirmed that subgenomic viral sequences are present and indicted that those sequences map to the viral genome between 0.32 and 0.43 map unit. (Author abstract) (22 Refs)

6. THE SITE OF INTEGRATION OF THE HERPES SIMPLEX VIRUS TYPE 1 THYMIDINE KINASE GENE IN HUMAN CELLS TRANSFORMED BY AN HSV-1 DNA FRAGMENT.

Kit S, Hazen M, Otsuka H, Qavi H, Trkula D, Dubbs DR
Div. Biochemical Virology, Baylor Coll. Medicine, Houston, TX, 77030
Int J Cancer; 28(6):767-776 1981

To analyze the site of integration of the herpes simplex virus Type I (HSV-I) thymidine kinase (TK) gene in biochemically transformed human cells, TK- HeLa(BU25) cells were transformed to the TK+ phenotype by a cloned, 2 kbp PvuII fragment of HSV-1 DNA. The transformed cells [HeLa(BU25)/TF pAGO PP3] were fused with mouse LM(TK-) cells, and human-mouse somatic cell hybrid clones (LH PP3 clones 1, 2, 3, 5 and 6) were isolated in HATG-ouabain selective medium. The HeLa(BU25)/TF pAGO PP3 cells and the LH PP3 hybrid clones expressed HSV-1-specific TK activity and a herpesvirus-associated nuclear antigen, and contained herpesvirus nucleotide sequences. Molecular hybridization experiments were carried out to map the HSV-I and flanking cellular nucleotide sequences in the biochemically transformed cells. TK- revertant subclones isolated by growing the LH PP3 clone 5 cells in BrdUrd (and diphtheria toxin) failed to form colonies in HATG medium, but retained HSV-I nucleotide sequences. Isozyme analyses on 21 gene-enzyme systems representing 21 human chromosomes revealed that all of the LH PP3 clonal lines expressed human hexosaminidase B, which has been assigned to chromosome 5, and all were sensitive to diphtheria toxin, which is also a marker for chromosome 5. Chromosome analyses showed that chromosome 5 was the only human chromosome present in mitoses of LH PP3 clone 5 cells and that human chromosome 5 was present in most of the mitoses of LH PP3 clone 1, 2, 3, and 6 cells. The latter clones also contained 1 or 2 additional human chromosomes in some of the cells. As expected from the molecular hybridization analyses, TK- revertants of LH PP3 clone 5 cells retained portions of chromosome 5 and expressed human hexosaminidase B. The results indicate that HSV-I nucleotide sequences were stably integrated in the biochemically transformed cells, most likely in human chromosome 5. (50 Refs)

7. REPLICATION OF VIRAL DNA SEQUENCES INTEGRATED WITHIN THE CHROMATIN OF SV40-TRANSFORMED CHINESE HAMSTER LUNG CELLS.

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Div. Biology, Kansas State Univ., Manhattan, KS, 66506
Cell; 26(2,part2):245-258 1981

To determine when during S phase integrated viral DNA sequences in several tsA SV40-transformed Chinese hamster cell clones replicate, we pulse-labeled cultures with BrdUrd and subsequently collected mitotic cells during sequential time intervals. Restriction endonuclease mapping indicated that each of the three SV40-transformed Chinese hamster lung cell clones contained a single viral DNA sequence at a different, but in each case unique, chromosomal site. DNA was extracted from each population of mitotic cells and then was resolved into dense, BrdUrd-containing and light, unsubstituted DNA fractions by cesium chloride gradient centrifugation. In each pair of samples obtained, we measured viral DNA sequences by soln hybridization using single-stranded SV40 32P-labeled DNA probes. Our results support the conclusions that specific genes within a mammalian DNA are programmed to replicate at particular times during S phase, and that the SV40 A gene product, large T antigen, programs integrated viral DNA sequences to replicate very early in S phase. The fractions of viral DNA replicated early in S phase appeared to correlate with each clone's content of functional large T antigen at permissive and nonpermissive culture temperatures. (Author abstract) (96 Refs)

8. STRUCTURAL ORGANIZATION AND BIOLOGICAL ACTIVITY OF MOLECULAR CLONES OF THE INTEGRATED GENOME OF A BALB/C MOUSE SARCOMA VIRUS.

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J Virol; 40(2):431-439 1981

BALB/c mouse sarcoma virus (BALB-MSV) is a spontaneously occurring transforming retrovirus of mouse origin. The integrated form of the viral genome was cloned from the DNA of a BALB-MSV-transformed nonproducer NRK cell line in the Charon 9 strain of bacteriophage lambda. In transfection assays, the 19-kilobase-pair (kbp) recombinant DNA clone transformed NIH/3T3 mouse cells with an efficiency of 3 x

10(4) focus-forming units per pmol. Such transformants possessed typical BALB-MSV morphology and released BALB-MSV after helper virus superinfection. A 6.8-kbp DNA segment within the 19-kbp DNA possessed restriction enzyme sites identical to those of the linear BALB-MSV genome. Long terminal repeats of approx 0.6 kbp were localized at either end of the viral genome by the presence of a repeated constellation of restriction sites and by hybridization of segments containing these sites with nick-translated Moloney murine leukemia virus long terminal repeat DNA. A continuous segment of at least 0.6 and no more than 0.9 kbp of helper virus-unrelated sequences was localized toward the 3' end of the viral genome in relation to viral RNA. A probe composed of these sequences detected six EcoRI-generated DNA bands in normal mouse cell DNA as well as a smaller number of bands in rat and human DNAs. These studies demonstrate that BALB-MSV, like previously characterized avian and mammalian transforming retroviruses, arose by recombination of a Type C helper virus with a well-conserved cellular gene. (Author abstract) (44 Refs)

9. COMPARISON BETWEEN THE VIRAL TRANSFORMING GENE (SRC) OF RECOVERED AVIAN SARCOMA VIRUS AND ITS CELLULAR HOMOLOG.

Takeya T, Hanafusa H, Junghans RP, Ju G, Skalka AM
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Mol Cell Biol; 1(11):1024-1037 1981

To gain information on the relationship between the src region of Rous sarcoma virus (RSV) (v-RSV) and cellular src (c-src), and clues to the origins of recovered avian sarcoma viruses (rASV), molecular clones were isolated containing src related sequences from the parental RSV, from rASV, and from c-src, the presumed progenitor of rASV. Molecular clones of viral DNA from rASV and its transformation-competent progenitor, the Schmidt-Ruppin A strain of RSV were constructed and analyzed. A 2.0-megadalton EcoRI fragment, containing the entire src gene from each of the clones was subcloned and characterized. The fragments were also used as probes to isolate recombinant phage clones containing the cellular counterpart of the viral src gene (c-src), from a lambda library of chicken DNA. Restriction endonuclease mapping of c-src revealed extensive similarity between the src region of RSV and rAVS, but striking differences between viral src's and c-src. Electron microscopic analysis of heteroduplexes between recovered virus src and c-src revealed a 1.8-kilobase homologous region. In the cellular gene, the homologous region was interrupted by seven nonhomologous region which is interpreted to be intervening sequences. Minimum length of c-src is estimated at 7.2 kilobases. The findings have implications concerning the mechanism of formation of recovered virus src and possibly other cell-derived retrovirus transforming genes. (58 Refs)

10. THE TRANSFORMING SEQUENCES OF AVIAN MYELOCYTOMATOSIS VIRUS (MC29).

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J Supramol Struct Cell Biochem; 16(2):193-207 1981

Avian myelocytomatosis virus (MC29) was isolated and characterized by recombinant DNA methods. DNA was obtained from the transformed nonproducer quail cell line Q5. This DNA was cloned using a library of phage prepared from a size-fractionated digest of Q5 DNA. Cloned DNA was then analyzed by Southern blotting of endonuclease digests and electron microscope examination of loops formed between the DNA and RNA from MC29 or helper virus. Cloned DNA consisted of approx 9.2 kilobases (kb), including approx 4 kb of viral DNA and 5.2 kb of quail cell DNA. The MC29-specific sequences, 5' helper-related sequences, and part of the envelope region were included in the viral portion. A cloned EcoRI fragment corresponded to the major band of EcoRI-cleaved DNA from Q5 cells that hybridized to viral sequences. Cloned DNA produced foci of transformed cells with high efficiency when transfected into NIH 3T3 cells, indicating that the MC29 sequences were functional. (31 Refs)

11. FATE OF VIRAL DNA IN NONPERMISSIVE CELLS INFECTED WITH SIMIAN VIRUS 40.

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Proc Natl Acad Sci USA; 78(11,part2):6638-6642 1981

Mouse cells are nonpermissive for simian virus 40 (SV40): replication of viral DNA is undetectable and progeny virions are not produced. Infection leads instead to the establishment of stably transformed cell lines in which viral DNA is covalently integrated into cellular DNA. We have followed the fate of SV40 DNA in infected mouse cells to define steps in viral DNA metabolism that precede integration. A novel high mol wt form of SV40 DNA is synthesized shortly after infection by a process sensitive to the inhibition of DNA replication. This DNA represents polymers in which viral genomes are organized as tandem 'head-to-tail' arrays. Recombination can be demonstrated with mutant viruses, but the recombination frequency is not high enough to account for the synthesis of polymers by recombination between infecting genomes. We conclude that polymers are synthesized by DNA replication and that they then recombine with one another. We believe that the polymers also recombine with cellular DNA and are thus the precursor to integrated viral DNA. Such a model accounts directly for the high frequency of tandemly duplicated viral insertions in transformed cells and also leads to experimentally testable predictions. (Author abstract) (37 Refs)

12. ONCOGEN LOCALIZATION IN DNA OF SIMIAN ADENOVIRUSES. I. IN VITRO TRANSFORMATION OF RAT CELLS WITH SV20 AND ITS DNA.

Parkhomenko II, DenisovaTS, Sitnikov BS, Bogatyrenko TN, Eliseeva LV

Lab. Physico-Chemical Basis of Oncology, Inst. Chemical Physics, Moscow, USSR

Tsitologiia; 23(8):932-936 1981

The results of comparative evaluation of in vitro transformation of kidney and embryo cells of Wistar rats after treatment with complete and incomplete simian adenovirus SV20 are reported. Defective virus provided transformation of 16% of infected colonies, compared with 1% transformation after treatment with complete virus. DNA from SV20 induced fibrosarcomas in 100% of newborn Syrian hamsters. (11 Refs) (In RUS)

13. LOCALIZATION OF ONCOGENE IN DNA OF SIMIAN ADENOVIRUSES. II. IDENTIFICATION IN SV20 DNA OF SPECIFIC FRAGMENT WITH TRANSFORMATION ACTIVITY.

Parkhomenko II, Denisova TS, Sitnikov BS
Lab. Physicochemical Basis of Oncology, Inst. Chemical Physics, Moscow, USSR
Tsitologiia; 23(9):1026-1030 1981

DNA of simian adenovirus SV20 was subjected to hydrolysis with the specific restriction endonucleases EcoRI, BamHI, XbaI, and HindIII. Transformation activity of DNA fragments produced by the BamHI was similar to that of the intact DNA. Absence of transformation activity in the fragments produced by the EcoRI indicated the left terminal position of the oncogene in the virus genome. (11 Refs) (In RUS)

14. TRANSFORMATION OF RAT FIBROBLASTS BY CLONED DEFECTIVE POLYOMA DNA.

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Arch Int Physiol Biochim; 89(3):225-233 1981

To define the sequence of polyoma (Py) DNA that is essential for cell transformation, defective Py DNA molecules were cloned in plasmid (p) BR322 and the recombinant plasmids were tested for their capacity to transform Fischer rat 3T3 cells in culture. Recombinant plasmids containing an intact proximal portion of the early region were able to transform. All DNA's capable of transforming cells contained an intact 5'-portion of the early region, ie, the region mapping between 70 and 100 map units. pH-df55, the recombinant lacking the DNA sequences extending from 92 to 24 map units, failed to transform. This shows the importance of DNA sequences encoding the C-terminal portion of Py middle T antigen in transformation. The frequency of transformation was of the same order for the three strains of Py virus. Transformation frequency varied little for recombinants containing an intact early region (such as pB4 and pH9) than those carrying only the proximal portion of the early region (such as pPA8). Furthermore, cells transformed by the proximal portion of the early region (PA series) grew as fast as those established by transfection with the complete Py genome (H series). Although the results do not exclude the possibility that small T antigen may play some role in transformation, they indicated that this antigen cannot be responsible for inducing the expression of the transformed phenotype. (28 Refs)

TRANSFORMATION GENE EXPRESSION AND REGULATION

15. CONTROL OF ADENOVIRUS EARLY GENE EXPRESSION: ACCUMULATION OF VIRAL MRNA AFTER INFECTION OF TRANSFORMED CELLS.

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J Virol; 40(2):358-366 1981

We studied the accumulation of viral mRNA in the presence of inhibitors of protein synthesis in an adenovirus Type 5-transformed cell line (line 293 cells). An analysis of the endogenous viral mRNA's and proteins revealed that only early regions 1A and 1B were expressed in uninfected 293 cells. However, viral mRNA's from early regions 2, 3, and 4, as well as mRNA's from early regions 1A and 1B, accumulated in 293 cells after infection with adenovirus Type 2. Cells treated with anisomycin before infection showed a drastic enhancement of mRNA from early region 4 compared with drug-free controls. This increase in viral mRNA was detected by using filter hybridization, S1 endonuclease mapping, and in vitro translation. The rate of transcription of early region 4 nuclear RNA also increased significantly in the presence of anisomycin. In contrast to the results with early region 4, the levels of cytoplasmic mRNA's from early regions 2 and 3 did not increase in cells treated with inhibitors. These results suggested that multiple virus encoded controls operate on the early regions of the adenovirus genome. (Author abstract) (31 Refs)

16. NUCLEOTIDE SEQUENCES OF 5' TERMINI OF ADENOVIRUS 2 EARLY TRANSFORMING REGION E1A AND E1B MESSENGER RIBONUCLEIC ACIDS.

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Biochemistry; 20(23):6640-6647 1981

The major 5'-terminal RNase T1 oligonucleotides derived from human adenovirus type 2 (Ad2) early regions E1a and E1b were characterized and sequenced. Poly(A+) polyribosomal RNA was isolated from Ad2-infected KB cells cultured 10 h in the presence of cycloheximide, the 5'-terminal m7Gppp was removed, and the 5'-OH of the penultimate 2'-O-methylated nucleoside was labeled with [gamma-32P]ATP by using polynucleotide kinase. 5'-32P-labeled poly(A+) RNA was hybridized to EcoRI-A, HpaI-E, and HpaI-C and to cloned fragments representing map positions 0-4.5, 4.5-8, 8-10.7, 8-17, and 17-31.5. Fragment-specific mRNA was digested with RNase T1, the resulting oligonucleotides were resolved by two-dimensional paper electrophoresis-homochromatography, and the 5'-terminal methylated oligonucleotides were characterized by nuclease P1 digestion and two-dimensional thin-layer chromatography. Two major 5'-terminal RNase T1 oligonucleotides were obtained from EcoRI-A-specific mRNA; these were characterized by RNase T2 digestion and two-dimensional thin-layer chromatography and were sequenced by partial nuclease P1 digestion and electrophoresis-homochromatography. These two oligonucleotides were mapped to E1a and E1b, respectively, by analysis of E1a- and E1b-specific mRNA. Their sequences are as follows: E1a, m7Gpp(m6)AmC(m)UCUUGp;
E1a,m7Gppp(m(6))AmC(m)UCUUGp;
E1b,m7Gppp(m(6))AmC(m)AUCUGp, in which the methylations shown in parentheses are partial. The E1a 5'-terminal oligonucleotide was found as a minor component of E1b mRNA, implying that mRNAs exist with both E1a and E1b sequences. Five other minor 5'-terminal oligonucleotides were observed in E1 mRNA, implying that transcription initiation is not always precise. Sequences corresponding to these two 5' termini were found at nucleotide positions 498-504 (E1a) and 1699-1705 (E1b) in the Ad2 DNA sequence, positions where the 5'-terminal region of E1a and E1b mRNAs has been mapped by nuclease gel analysis and electron microscopic visualization. (50 Refs)

17. TWO POLYOMA VIRUS GENE FUNCTIONS INVOLVED IN THE EXPRESSION OF THE TRANSFORMED PHENOTYPE IN FR 3T3 RAT CELLS: I. LOCALIZATION OF TRANSFORMATION MAINTENANCE FUNCTION IN THE PROXIMAL HALF OF THE LARGE T CODING REGION.

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Virology; 114(2):489-500 1981

The hypothesis is presented that the expression of a fully transformed phenotype in FR 3T3 rat fibroblast cells transformed with polyoma virus requires two viral gene products. One is the membrane-associated middle T protein (as previously recognized in a number of laboratories). A second necessary function is dependent on an N-terminal region of the large T protein. It can be exerted either by the full-size large T protein (105K), or by truncated forms deleted in the C-terminal region. This hypothesis is supported by the results of a complementation analysis using the tsa mutant, which affects only the complete large T protein, and a cloned segment of the viral DNA that codes only for the N-terminal part of large T (BamHI-EcoRI fragment of an hrt (NG 18) deletion). Results show that this subgenomic fragment is able to complement the tsa defect for the maintenance of the transformed state, but not for its establishment. (Author abstract) (39 Refs)

18. TWO POLYOMA VIRUS GENE FUNCTIONS INVOLVED IN THE EXPRESSION OF THE TRANSFORMED PHENOTYPE IN FR 3T3 RAT CELLS: II. THE PRESENCE OF THE 56K MIDDLE-T PROTEIN IN THE CELL MEMBRANE IS NOT SUFFICIENT FOR MAINTENANCE.

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Virology; 114(2):501-506 1981

Rat fibroblast cells transformed with the tsa mutant of polyoma virus (Type N) exhibit a fully transformed phenotype when grown at low temperature and synthesize the three early viral proteins, large T, middle T, and small T. After a shift to the restrictive temperature, these cells revert to the normal phenotype. They still synthesize the middle T protein, undistinguishable from that present in phenotypically transformed cells on the basis of its apparent mol wt, association with cell membrane, and in vitro phosphorylation. Therefore, the synthesis of middle T and its association with the cell membrane do not appear to be sufficient conditions for the expression of the transformed phenotype. (Author abstract) (23 Refs)

19. THE SRC GENE PRODUCT (PP60SRC) OF AVIAN SARCOMA VIRUS RAPIDLY INDUCES DNA SYNTHESIS AND PROLIFERATION OF CALCIUM-DEPRIVED RAT CELLS.

Durkin JP, Boynton AL, Whitfield JF
Animal and Cell Physiology Group, Natl. Res. Council Canada, Ottawa, Ontario K1A OR6, Canada
Biochem Biophys Res Commun; 103(1):233-239 1981

Calcium-deprived tsLA23-NRK cells are reported to be blocked near the G1/S boundary of the cell cycle at 40 C, a temperature non-permissive for neoplastic transformation. Such arrested cells rapidly initiated DNA synthesis and resumed proliferating in calcium-deficient medium when the temperature was lowered to 36 C, a level permissive for the production of active pp60src and neoplastic transformation. In contrast, previous studies had shown that calcium-deprived wtB77-NRK cells grew rapidly and continuously at either 40 C or 36 C, while uninfected NRK cells were unable to proliferate at either temperature in calcium-deficient medium. The product of the src transforming gene of avian sarcoma virus may thus act near the G1/S border to rapidly bypass or directly stimulate a normally calcium-dependent process needed for the initiation of DNA synthesis. pp60src thus allows neoplastic, avian sarcoma virus-infected NRK cells to proliferate in calcium-deficient medium which does not support the proliferation of non-neoplastic counterparts. This work supports the suggestion that changes in protein kinase activities are responsible for the ability of a wide variety of transformed avian, bovine, rodent and human cells to proliferate in calcium-deficient medium. (21 Refs)

20. CHARACTERISTICS OF AVIAN SARCOMA VIRUS STRAIN PRCIV AND COMPARISON WITH STRAIN PRCII-P.

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Virology; 114(2):451-462 1981

Avian sarcoma virus strain Poultry Research Center IV (PRCIV) is highly oncogenic in chickens and transforms chicken embryo fibroblasts in culture. It is defective in replication, unable to code for complete functional products of the three essential viral genes gag, pol, or env. Nonproducing cells transformed by PRCIV lack the transforming protein of Rous sarcoma virus, pp60src, but synthesize a new transformation-specific protein of 170,000 mol wt. This P170 contains partial gag sequences, probably at its N-terminus and transformation-specific, cell-derived sequences, probably in the C-terminal portion of the molecule. In two-dimensional tryptic peptide maps P170 of PRCIV is indistinguishable from the transformation-specific protein P170 of the previously described PRCII-p. Both P170 proteins also contain all but one tryptic peptide of the transformation-specific gag-linked protein P105 found in cells transformed by avian sarcoma virus PRCII. The P170 proteins of PRCIV and PRCII-p have an associated tyrosine-specific kinase activity similar to P105 of PRCII. All three agents, PRCII, PRCII-p, and PRCIV, belong to Class II of avian sarcoma viruses. In cells transformed by PRCIV or PRCII-p secondary gag-linked transformation-specific proteins of less than 170,000 mol wt are sometimes seen, but limited in vivo and in vitro passage of the viruses shows the P170 to be a stable characteristic of PRCIV and PRCII-p transformation. The genomic RNA of PRCIV and PRCII-p sediments at 30 S corresponding to a size of about 6.1 kilobases. (Author abstract) (35 Refs)

21. TUMOR ASSOCIATED ANTIGENS AND TRANSFORMATION PROTEINS OF FELINE RETROVIRUSES (MEETING ABSTRACT).

Essex M, Chen AP, Mikami T
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

Cats naturally exposed to feline leukemia virus (FeLV) or feline sarcoma virus (FeSV) mount a humoral antibody response that is directed to tumor associated antigens. Antigens thus far identified as targets for this immunosurveillance-correlated response that are distinct from the virion structural proteins include an antigen of about 70,000 daltons on lymphoid tumor cells (FOCMA-L) and a polyprotein of 84,000 daltons or 110,000 daltons, depending on the strain of virus, on FeSV-transformed fibroblasts. Healthy cats that are exposed to FeLV under natural conditions in leukemia cluster households develop high titers of humoral antibodies to FOCMA. Both adult and young cats that are introduced to such FeLV-exposure environments usually seroconvert to develop FOCMA antibodies within a few mo. When all FeLV-excretor cats are removed from such environments no additional seroconversions occur. However, cats that already have significant humoral antibody titers at the time FeLV-excretor cats are removed maintain humoral antibody titers without re-exposure to FeLV for at least several yr. This suggests that such cats either maintain FeLV in a latent, but not a widely dispersed or excreted form, or that such cats harbor a population of FeLV-altered FOCMA positive cells that are maintained at low levels by an immunosurveillance response. The antigen found in fibroblasts transformed with FeSV is representative of a class of 'gag-x' proteins which are typical of many defective transforming retroviruses in that they contain gag peptides linked to a transformation specific portion designated 'x'. The 'x' portion is encoded by 'one' or 'fes', a member of the set of highly conserved cell genes that become inserted into replication defective retroviruses when they acquire the ability to transform fibroblasts in vitro. Cats inoculated with their own FeSV-transformed cells following in vitro cultivation and transformation develop a humoral antibody response to 'x' of 'gag-x', as do some highly immune cats that have apparently only been exposed to FeLV. When FeSV is used to induce widely different types of tumors, such as melanomas of neuroectodermal origin and fibrosarcomas of mesodermal origin, the same 'gag-x' is expressed concordantly with the malignant phenotype. (3 Refs)

22. EXPRESSION OF TUMORIGENICITY IN HUMAN EPITHELIAL TUMOUR X TUMOUR HYBRIDS (MEETING ABSTRACT).

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Cell Biol Int Rep; 5(SupplA):22 1981

Three pseudo-diploid clones, beta, 8D and 5E have been isolated from a human bla dder carcinoma cell line and characterized for the chromosome constitution, growth in agar and tumorigenicity in nude mice. All three clones were chromosomally unique, and tumorigenic but showed varying ability to grow in agar (beta, 0.5%; 8D, 3%; 5E, 9% efficiency). Hybrids and homokaryons were isolated from fusions between the clones beta x 8D and 5E x 8D. Each fusion product was analyzed cytogenetically and for the ability to grow in agar and produce tumors in nude mice. Chromosome loss did occur in some of the fusion products but the max loss was 12 chromosomes. All the hybrids grew in agar but with varying efficiencies; some hybrids showed the high and low colony forming efficiency seen in the parental clones while others had an intermediate ability to grow in agar. All the hybrids produced tumors in nude mice. Although all hybrids retained a transformed phenotype some of the homokaryons did not. Only the 5E/5E homokaryons grew in agar and produced tumors. One 8D/8D homokaryon could not be grown in agar but it did produce tumors in nude mice. Both of the beta/beta homokaryons that were isolated had a low colony forming ability (0.5% efficiency) and neither produced tumors when first inoculated into nude mice. One of the beta/beta homokaryons did produce tumors in 2/4 mice later at passage 17. No correlation between tumorigenicity and absence or presence of specific chromosomes could be established. (no Refs)

GENETIC AND OTHER HOST FACTORS WHICH MODULATE ONCOGENIC TRANSFORMATION

23. POSSIBLE ROLE OF GENETIC CELL VARIANTS IN THE VIRAL INDUCTION OF MOUSE MAMMARY TUMORS.

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In Vitro; 17(9):805-810 1981

Out of three attempts to induce neoplasia in normal C57Bl mammary epithelial cells with the mouse mammary tumor virus (MuMTV) only one presented signs of tumorigenicity. Immunofluorescence showed that virus synthesis took place in all three sublines but tumorigenicity as detected by cell aggregation viability (CAV) and transplantation into syngeneic mice failed to occur in two of them. By comparison, cells from a BALB/c spontaneous mammary tumor that do not express MuMTV were 100% tumorigenic, whereas cells from a BALB/cfC3H tumor with a 95% virus-producing cell population had a normal CAV and were tumorigenic only in 60% of the test animals. This lack of correlation suggested that many of the virus-producing cells were not neoplastic and that neoplasia might occur under virus stimulation only if a restricted population of genetic cell variants existed. Accelerated tissue culture passages of virus-free C57Bl and BALB/c normal mammary cells resulted in their spontaneous neoplasia at Passages 23 and 50, respectively; when duplicated cells cryopreserved in early passages were revived and cultivated in the same manner, neoplasia occurred at Passages 27 and 58. The similarity of the passage numbers appears to confirm the existence of genetic cell variants among the normal cell population. (Author abstract) (16 Refs)

24. INCIDENCE AND PHENOTYPIC HETEROGENEITY OF MOLONEY VIRUS-INDUCED LEUKEMIAS: A MULTIGENIC CONTROL.

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Blood Cells; 7(2):301-311 1981

Adults of seven inbred mouse strains were inoculated with Moloney leukemia virus (MuLV). Incidence of viremia after 2 mo ranged from 1.8% in B6 to 87% in BALB/c while incidence of leukemia after 6 mo ranged from 0% in NZB and DBA/2 to 97% in BALB/c. In individual mice, the host-virus relationship was studied further as to degree of viremia, appearance of leukemia, organ involvement, and surface phenotype of leukemic cells. The viremia was controlled by H-2 and non-H-2 genes. Three of the H-2 genes in the I and D or T region of the major histocompatibility complex (MHC) behave like immune-response genes which control the specific antiviral immune response. Other gene(s) outside the MHC also affected virus production. Both sets influenced leukemia incidence, since leukemias occurred only in highly viremic strains. Additional non-H-2 genes not involved in viremia, were determinants in induction of malignancies, since some sensitive strains did not become leukemic despite high levels of virus. The anatomical type of MuLV-induced leukemias varied according to the non-H-2 background. As an example, most leukemias in B10 congeneic mice involved thymus and were frequently limited to this organ, whereas BALB mice preferentially developed splenic leukemias. In a given strain, leukemias arising in different individuals frequently expressed different phenotypes. It is concluded that MuLV-induced leukemia is a multistep process in which virus production is necessary, but is not sufficient in itself, to induce malignant transformation. (20 Refs)

25. XENOTROPIC TYPE C VIRUS EXPRESSION IN MURINE THYMOMAS INDUCED BY RADIATION OR 3-METHYLCHOLANTHRENE.

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Virology; 114(2):580-584 1981

Thymic lymphoma incidence and thymic expression of MuLV with xenotropic infectivity was monitored in AKR, RF and reciprocal F1 mice of the AKR x RF cross after treatment with either gamma radiation or the chemical carcinogen 3-methylcholanthrene (MCA). These two inbred strains and the F1 hybrids developed similarly high incidences of thymoma, and lymphomatous cells from AKR mice and (AKR male x RF female)F1 mice were observed to be expressing MuLV with xenotropic host range. However, lymphoma cells from R F mice and (RF male x AKR female)F1 mice did not shed xenotropic MuLV. Thymic xenotropic virus expression was therefore not correlated with a high incidence of radiation or chemically induced thymoma, but rather appeared to be a phenotype genetically transmitted by AKR mice to F1 mice of the AKR x RF cross as a dominant trait in induced thymomas. In addition, a maternal effect on thymic xenotropic virus expression in induced thymomas was observed by the comparison of reciprocal F1 hybrids in this cross. (Author abstract) (7 Refs)

26. SUPPRESSION OF TUMORIGENICITY IN CYBRIDS.

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J Supramol Struct Cell Biochem; 16(1):75-82 1981

Cytoplasmic control of tumorigenicity was studied. Cytoplasmic hybrids (cybrids) were produced by enucleation of cells from the nontumorigenic cell line A-MT-BU-A1 (AMT) and fusion of the remaining cytoplasm with whole cells from cell the tumorigenic cell line C17-S1-D-T894 (984 C1 10). Clones of AMT, 984 C1 10, and cybrid cells were then tested for tumorigenicity in BALB/c nude mice. All of 14 984 C1 10 clones tested produced tumors in mice and were unable to differentiate into skeletal muscle (SM) in vitro. AMT subclones did not form tumors and did not differentiate into SM in vitro. Of 27 cybrid subclones 17 were able to differentiate in vitro. One differentiating and one nondifferentiating cybrid clone produced undifferentiated sarcomas in nude mice. Results indicate that cytoplasmic factors can produce long-term, heritable effects on tumorigenicity, and that such factors may suppress tumorigenicity in spontaneously, but not virally, transformed cell lines. (26 Refs)

27. ABELSON VIRUS-INFECTED CELLS CAN EXHIBIT RESTRICTED IN VITRO GROWTH AND LOW ONCOGENIC POTENTIAL.

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J Virol; 40(2):577-584 1981

We have designed a method for growing bone marrow cells infected with Abelson murine leukemia virus which permits examination of target cell growth early after infection. This culture system increases the efficiency of target cell growth by favoring rapid growth of a mixed population of adherent cells in the primary culture. The nonadherent Abelson virus-infected cell populations expressed pre-B-cell differentiation markers characteristic of Abelson virus-transformed cells (mu-heavy chains of Ig M and terminal deoxynucleotidyltransferase). Early after infection, these cell populations exhibited restricted in vitro and in vivo growth properties which differed from those of an established Abelson virus-transformed cell line, 2M3. These included a marked dependency upon the adherent cell layer for growth and viability, a lower efficiency of agar colony formation, and a lower capacity for tumor production in syngeneic animals. Growth of the early populations could be maintained in the absence of the adherent cell layer by using conditioned medium from long-term adherent cell cultures established in the absence of viral infection. After passage of the populations for several wk, the in vitro growth properties gradually shifted toward that of the 2M3 cell line. Twelve-wk-old populations grew independently of the adherent cell layer and showed an increased efficiency of agar colony formation. These data indicate that many lymphoid target cells exhibit an intermediate transformed phenotype when infected with Abelson virus. Growth of these cells in culture is mediated via a synergistic interaction between intracellular expression of the viral transforming gene and an exogenous growth-promoting activity which can be provided by cultures of adherent bone marrow cells. (Author abstract) (31 Refs)

28. GENETIC STUDY OF N-NITROSOMETHYLUREA-INDUCED THYMIC LYMPHOMA IN INBRED MICE (MEETING ABSTRACT).

Mayer A

No affiliation given

Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

Mice of various inbred strains were injected ip with the chemical carcinogen N-nitrosomethylurea to induce thymic lymphoma. All the strains developed this specific neoplasia to high incidences, but marked differences were observed between strains with respect to the duration of the latent period, which extended from exposure to the carcinogen at 5-9 wk of age until overt development of thymic lymphoma (indicated by labored breathing) followed shortly thereafter by death. The RF/J and AKR/J strains showed the shortest latent periods, with deaths occurring from 12 to 18 wk of age. The 129 and C57BL/6 strains were characteristic of the longer-latency type, with deaths occurring from 16 to 30 wk of age. In two crosses tested, the AKR x 129 and the 129 X RF, the short-latency phenotype was observed to be dominant. Data from the (129 x RF) F1 x 129 backcross will be presented to indicate the number of loci involved in the short-latency phenotype, and to discern whether endogenous ecotropic murine leukemia virus and/or the H-2 locus plays a role in this phenomenon. (no Refs)

EXPERIMENTAL MODULATION OF ONCOGENIC TRANSFORMATION

29. THE INFLUENCE OF CELLULAR PROLIFERATIVE HISTORY ON THE SUSCEPTIBILITY TO ONCOGENIC TRANSFORMATION.

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J Cell Physiol; 109(2):317-322 1981

Survival and transformation of cells exposed to UV light in the same metabolic state but differing only in their prior proliferative history were studied with C3H mouse embryo-derived 10T/1/2 clone 8 cells. The cells were serially transferred from passage 11 to 15 with 5 x 10(4) cells seeded per 60-mm dish at each passage. One group was passaged as soon as confluence was reached, while two others were kept for 3 or 6 days in confluence at each passage before subculture. There was a progressive selection in all three cases for cells which cloned at higher efficiencies. From passage 11 to 15, there was a slight selection for shorter population doubling times (18.8 hr at passage 10, and 17.0, 17.0, and 17.3 hr at passage 15 after day 0, day 3, and day 6 passage regiments). The saturation densities were 1.1 x 10(6) cells per 60-mm dish at passage 10, and 1.3 x 10(6), 1.2 x 10(6), and 1.1 x 10(6) for the three groups at passage 15, respectively. UV light survival curves for day 0, day 3, and day 6 cells at passage 15 demonstrated slopes of the straight-line portions of-0.32,-0.31, and-0.35 square meter/Joule, respectively. The transformation frequencies for the day 3 and day 6 groups were eight-fold lower than that of the day 0 group. These results suggest that the susceptibility of these cells to transformation is influenced by their proliferative history; intermittent growth quiescence in previous passages decreased this susceptibility. (28 Refs)

30. PROPERTIES OF A SARCOMA-GROWTH-FACTOR-LIKE PEPTIDE FROM CELLS TRANSFORMED BY A TEMPERATURE-SENSITIVE SARCOMA VIRUS.

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J Cell Physiol; 109(1):143-152 1981

Peptides resembling sarcoma growth factor (SGF) that were produced by virally transformed cells in vitro were characterized. Normal rat kidney (NRK) cells and 3T3 mouse cells were transformed by Moloney sarcoma virus (MSV) or Kirsten sarcoma virus (KiSV). SGF-like factors were obtained from serum-free conditioned media from the cell cultures. Nontransformed cells produced no such factors. The major activity, regardless of cell species or virus type, was produced by a factor with an apparent mol wt of 10,000. Carboxymethyl cellulose chromatography produced similar elution profiles in all cases. Growth factor produced by NRK cells transformed by wild-type KiSV had similar temperature sensitivity to growth factor produced by NRK cells transformed by a temperature sensitive mutant of KiSV. Neither growth factor was temperature-sensitive under the conditions of the assay. THE SGF-like factors produced by transformed cells are apparently produced by cellular genes that are not expressed in the absence of virus. (21 Refs)

31. RESPONSIVENESS OF FETAL RAT BRAIN CELLS TO GLIA MATURATION FACTOR DURING NEOPLASTIC TRANSFORMATION IN CELL CULTURE.

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Acta Pathol Microbiol Scand [A]; 89(5):393-402 1981

The effect of partially purified extracts from adult pig brains containing a glia maturation protein factor (BE) has been investigated on neural cells during carcinogenesis. Pregnant BD IX-rats were given a single transplacental dose of the carcinogen ethylnitrosourea (EtNU) on the 18th day of gestation. The brains of the treated fetuses were transferred to cell culture and underwent neoplastic transformation with a characteristic sequence of phenotypic alterations which could be divided into five different stages. During the first 40 days after explanation (Stage I and II) BE induced morphological differentiation of epithelioid neural cells into astrocytes. this occurred in carcinogen treated cells as well as in untreated control cultures. At the same time cells with astrocyte morphology showed accumulation of glial fibrillary acidic protein (GFA) as tested by indirect immunofluorescence with monospecific antibodies against GFA. Thereafter, in the EtNU pre-treated cultures an increased number of cells with astrocyte morphology was seen, and BE further increased the number of cells with long cytoplasmic processes. Control cells were GFA negative, while some few strongly, as well as many weakly, positive cells were seen after treatment with BE (Stage III). At the later stages of neoplastic transformation the effect of BE became gradually less, and in tumorigenic cells which occurred after about 200-300 days, only a slight morphological change took place in a few cell lines. No appreciable effect on GFA-content was seen any longer, although some few weakly GFA positive cells could be observed in all permanent cell lines. Fetal rat brain cells therefore seem to become less responsive to this differentiation inducer during neoplastic transformation in cell culture. (Author abstract) (36 Refs)

32. TUMOR PROMOTERS INDUCE THE SYNTHESIS OF A SECRETED GLYCOPROTEIN IN MOUSE SKIN AND CULTURED PRIMARY MOUSE EPIDERMAL CELLS.

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Carcinogenesis; 2(10):971-976 1981

Effects of tumor promoters and anti-promoters on synthesis and secretion of a 35,000 dalton transformation-dependent secreted glycoprotein (major excreted protein, MEP) by primary mouse epidermal cells were investigated. 12-O-Tetradecanoylphorbol-13-acetate (TPA) increased synthesis and secretion of MEP, an effect that was maximal at 6 hr. This time course is consistent with an effect of TPA on transcription of MEP messenger RNA. The induction of MEP synthesis was very sensitive to TPA, with half-maximal stimulation (at 3 nanog/ml or less). TPA also induced MEP synthesis in mouse skin in situ. The anti-promoters lidocaine and retinoic acid had no effect on basal MEP synthesis or secretion, or on TPA stimulation. Fluocinolone acetonide decreased basal levels of MEP synthesis without blocking TPA-induced M EP synthesis. The data suggest that the effects of the three anti-promoters are not mediated via an alteration in MEP synthesis or secretion and that an increase in MEP synthesis per se is not sufficient for promotion. (33 Refs)

33. ONCOGENICITY OF HEAT-INACTIVATED SIMIAN ADENOVIRUS SA7.

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Arch Virol; 69(3/4):189-196 1981

Simian adenovirus SA7 heated for 30 min at 70 C retained part of its ability to induce tumors in newborn hamsters. Tumors were also induced by DNA extracted from the heated virus. However, neither residual replicating, ie cytopathogenic, nor transforming and T-antigen-inducing activities could be detected in vitro in CV-1 and hamster embryo cells inoculated with the heated virus. The results are discussed in terms of a possible release of viral nucleic acid at the high temperature. They also show that current tests for effective virus inactivation based exclusively on the recognition of replicating virus should be reevaluated. (Author abstract) (19 Refs)

34. SPECTRAL DEPENDENCIES OF KILLING, MUTATION, AND TRANSFORMATION IN MAMMALIAN CELLS AND THEIR RELEVANCE TO HAZARDS CAUSED BY SOLAR ULTRAVIOLET RADIATION.

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Cancer Res; 41(12):4916-4924 1981

Using germicidal lamps and Westinghouse sunlamps with and without filtration, the effectiveness of UV and near-UV light in inducing molecular and cellular changes was measured. Cell survival and the induction of resistance to 6-thioguanine or to ouabain were measured with V79 Chinese hamster cells, cell survival and neoplastic transformation were measured with C3H mouse 10T1/2 cells, and the induction of pyrimidine dimers containing thymine was measured in both cell lines. The short-wavelength cutoff of the sunlamp emission was shifted from approx 290 nm (unfiltered) to approx 300 and approx 310 nm by appropriate filters. Although it was found that the efficiency with which all end points were induced progressively decreased as the short-wavelength cutoff was shifted to longer wavelengths, the rates of decrease differed appreciably. For example, doses of near-UV light longer than approx 300 nm that were effective in mutating or in transforming cells were ineffective in killing them. In respect to pyrimidine dimer induction, several but not all cellular end points were induced by dose ratios of sunlamp light (short-wavelength cutoff, approx 290 nm) to germicidal lamp light (254 nm) in fairly close accord with the doses required to produce equivalent proportions of dimers. However, for near-UV light having cutoffs at longer wavelengths, the biological action observed was appreciably greater than what would be predicted from the proportion of dimers induced. From the latter observation, it is inferred that increasing intensities of short-wavelength UV light, as would be expected from reductions in stratospheric ozone around the earth, would result in smaller increases in biological action, eg, skin cancer, compared to current levels of action than would be predicted from an action spectrum completely corresponding to that of a pyrimidine dimer induction spectrum in DNA. (Author abstract) (45 Refs)

35. ENHANCING EFFECT OF MURINE LEUKEMIA VIRUS ON FIBROBLAST TRANSFORMATION BY NORMAL BALB/C DNA FRAGMENTS.

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Haematol Blood Transfus; 26:479-482 1981

Mechanically fragmented normal BALB/c mouse DNA was used to transform NIH/3T3 cells. Primary transformation occurred at a low frequency, but secondary transfections with DNA isolated from the transformed cells was highly efficient. Appropriate controls were used to ensure the DNA specificity of this phenomenon. No reverse transcriptase activity was found in any of the transformed cell lines. All six transformed cell lines were anchorage independent (they grew well in soft agar) and all were oncogenic when injected ip into newborn athymic BALB/nude mice. Five of the six cell lines produced fibrosarcomas within 3 wk when injected sc into 3-wk-old BALB/c mice. No transforming virus could be rescued after infection of the cell lines with Moloney strain murine leukemia virus (MuLV). Antibody raised in C57BL mice against syngeneic Abelson MuLV (A-=MuLV) reacted with a variety of A-MuLV-transformed cells but not with any of the NIH/3T3 cells infected with Moloney MuLV. Preinfection of the NIH/3T3 cells with wither Rauscher or Moloney MuLV enhanced transformation by normal cell DNA fragments (transformation occurred both earlier and with a higher efficiency). These and previously reported finding support the idea that the insertion of cellular genes in transposed sequence into the cellular DNA may result in oncogenic transformation, perhaps due to their being inserted near active promoter sequences. It is further hypothesized that preinfection with MuLV produces a semitransformed state in 3T3 cells or that MuLV provides the infected cells with highly active promoter sequences. (7 Refs)

36. ANGIOGENESIS AND PREDICTION OF SARCOMA FORMATION BY PLASTIC.

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Cancer Res; 41(12):5060-5063 1981

The capacity to induce new formation of capillaries was tested in cells attached to plastics. It is known that large plastic coverslips implanted sc in CBA mice produce sarcomas more rapidly and in a greater number than do small coverslips. We observed that within a few wk after implantation the cells attached to the large coverslips showed an angiogenic capacity about 5-fold greater than that of the cells attached to the small coverslips. Months before a sarcoma was evident, angiogenesis induced by the cells attached to the large coverslips predicted the high risk of neoplastic transformation by large coverslips. (Author abstract) (29 Refs)

37. EPIDERMAL GROWTH FACTOR: I. MORPHOLOGICAL EFFECTS ON HUMAN CARCINOMA CELLS. II. RELATEDNESS OF THE EGF RECEPTOR-KINASE TO A VIRAL TRANSFORMING PROTEIN.

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Vanderbilt University, Nashville, TN, 37203
Diss Abstr Int [B]; 42(4):1272-B 1981

This dissertation is divided into two parts, each concerned with the interaction of epidermal growth factor (EFG) with A-431 human epidermoid carcinoma cells. EGF induces rapid and dramatic shape changes in these cells; the exact nature of these changes depends on whether Ca++ is present in the medium. After several hr, as cells retracting at the edges of colonies pile up on top of each other, multilayered colonies are formed. This multilayered morphology persists for several days in the presence of EGF, but is freely reversed upon removal of EGF from the medium. The second part of the dissertation concerns the interaction of affinity-purified EGF receptor, prepared from A-431 cells, with antibodies to the transforming protein, pp60src, of Rous sarcoma virus (RSV). This study was initiated, in part, because (a) the EGF-induced morphological changes described above are similar to RSV-induced cell shape changes and (b) both pp60src and the partially purified EGF receptor possess tyrosine-specific protein kinase activity, the latter being stimulated by EFG. The EGF-stimulated kinase, like pp60src, specifically phosphorylates the heavy chain of anti-pp60src IgG; this phosphorylation occurs on tryosine and is stimulated by EGF. However, neither the receptor nor its associated kinase activity are precipitated by these antisera, even those able to precipitate the normal cellular homologue of pp60src (pp60sarc). These results suggest that while the EGF-stimulated kinase is probably not pp60sarc, it may be related to that enzyme. (no Refs)

38. PROGRESSION INTO 'DEEP' RESTING STATES REQUIRED FOR CARCINOGENIC TRANSFORMATION IN CULTURES OF C3H/10T1/2 CELLS (MEETING ABSTRACT).

Miska D, Bosmann HB
University of Rochester, Rochester, NY
Toxicologist; 1(1):154 1981

We have previously shown that confluent cultures of C3H/101/2 cells progress into deeper G0 states with culture age as indicated by lengthened prereplicative lag times after serum step-up. This progression is here shown to be influenced both by the serum concentration and the medium renewal frequency. Conditions that block this progression also inhibit carcinogenic transformation. Cells were seed ed at 100/1.6 mm well in Eagle's Basal Medium containing 10% heat-inactivated fetal calf serum, and treatment wells received 1.0 or 5.0 ug 3-methylcholanthrene in 0.5% acetone from 24-48 hr. At confluency the wells were divided into 4 groups by serum concentration and renewal frequency: 10%-4d, 10%-1d, 3%-4d, 3%-1d. Cell counts of representative untreated wells were made daily from seeding until day 27. The 3%-4d, 3%-1d, and 10%-4d, groups achieved steady-state densities of 1.1, 2.0, and 2.3 x 10(5) cells/well, respectively, but the 10%-1d group continued to grow and had a density of 7.0 x 10(5) cells at 27 days. Transformation, as measured by type III foci 42 days after seeding, was completely inhibited in this group. Transformation in the other groups was independent of density but was influenced by the carcinogen's concentration. At 42 days the GO depth for each group was measured by nuclear labeling with [3H]-thymidine after serum step-up. The groups that showed transformation had progressed into GO beyond what is seen in freshly confluent cells, whereas the untransformed 10%-1d group had not, indicating that the cultures must progress into deep resting states for carcinogenic expression. (no Refs)

39. RELEVANCE OF ENDOGENOUS TYPE C RETROVIRUS ON M-MSV ONCOGENESIS: EXPRESSION OF ENDOGENOUS M-MULV AND NATURAL ANTIBODY PRODUCTION ASSOCIATED WITH RESISTANCE TO TUMOR INDUCTION (MEETING ABSTRACT).

Chieco-Bianchi L, E'Andrea E, De Rossi A, Salmi R
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

Previous work has shown that mice which express high titers of endogenous type C ecotropic retrovirus are partially or totally resistant to tumor induction by Moloney murine sarcoma virus (M-MSV). To further investigate the role of endogenous virus in M-MSV oncogenesis, BALB/Mo mice, which carry the Moloney murine leukemia virus (M-MuLV) as an endogenous, genetically transmitted virus on BALB/c background, were studied. Groups of BALB/Mo and conventional BALB/c mice were injected im with M-MSV at different ages (3-6 wk). As expected BALB/c mice were fully susceptible to M-MSV tumor induction, and all developed tumors in one wk. On the contrary, in 6 wk old BALB/Mo mice tumors appeared only in 17% of mice and after a prolonged latent period. A certain degree of resistance was also present in 3 wk old BALB/Mo mice as revealed by a longer tumor latency than in age-matched BALB/c mice. To elucidate the possible mechanisms underlying the resistance, BALB/Mo mice were tested for M-MuLV expression at different ages by the UV-XC plaque test. It was found that tumor resistance paralleled the time course of M-MuLV activation since mice became virus positive starting at 2 wk of age and all mice were positive at 8 wk. Furthermore, normal BALB/Mo sera tested for antibody production against M-MuLV surface determinants, using a 125I-protein A binding assay, disclosed a relevant degree of binding capacity already present in some 3-4 wk old individuals and which increased further with age. An additional study carried out in female BALB/J x male (BALB/J x BALB/Mo) Bcl hybrids also showed a closely correlated pattern between M-MuLV expression, antibody production and M-MSV tumor resistance. (1 Ref)

40. DIMETHYLSULFOXIDE-INDUCED MODIFICATION OF ONCODEVELOPMENTAL (AFP) AND LATE-DIFFERENTIATION (ALBUMIN) GENE EXPRESSION IN AN ESTABLISHED LINE OF MOUSE HEPATOMA CELLS (MEETING ABSTRACT).

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Oncodev Biol Med; AbstractsBook,1:30 1981

The effect of the differentiation-inducing agent dimethylsulfoxide (DMSO) on the synthesis of alpha-fetoprotein (AFP) and albumin (ALB) was evaluated using in vitro-propagated mouse hepatic tumor cells (BW77-1). DMSO-treated cells exhibited increased intra- and extra-cellular accumulations of both proteins compared to control cultures. The ALB contribution to total cellular protein increased with exposure of BW77-1 cells to progressively higher concentrations of DMSO in the growth medium. In contrast, while a considerable enhancement in hepatoma cell-associated AFP was noted upon incubation in 0.5% DMSO compared to non-DMSO-treated hepatocytes (65% increase), the AFP content in total cellular protein declined slightly upon exposure of BW77-1 cells to DMSO in final concentrations of more than 0.5%. Inhibition of the in vitro expression of certain growth properties ascribed to the transformed state as a consequence of exposure of BW77-1 cells to increasing levels of DMSO in the growth medium was found to be correlated with changes in the progression of the hepatoma cell population through the cell cycle and with a gradually enhanced capacity for synthesis of a differentiated hepatocyte gene product (ALB) and concomitant restricted expression of an oncodevelopmental antigen (AFP). (no Refs)

BIOCHEMICAL AND MOLECULAR BIOLOGICAL STUDIES OF TRANSFORMED PHENOTYPE

41. QUANTITATION AND CHARACTERIZATION OF A SPECIES-SPECIFIC AND EMBRYO STAGE-DEPENDENT 55-KILODALTON PHOSPHOPROTEIN ALSO PRESENT IN CELLS TRANSFORMED BY SIMIAN VIRUS 40.

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Proc Natl Acad Sci USA; 78(11,part2):6953-6957 1981

A 55-kilodalton (kDal) protein was detected recently in primary cultures of day 12 mouse embryos by immunoprecipitation with serum from simian virus 40 (SV40) tumor-bearing hamsters (T serum). Preliminary evidence suggested that this protein was similar to a cellular 55-kDal protein induced after SV40 transformation of mouse cells. We now show that specific approx 55-kDal [35S]methionine-labeled proteins precipitate from primary cultures of midgestation mouse, rat, and hamster embryos on addition of T serum or monoclonal antiserum prepared against the SV40-induced mouse 55-kDal proteins. The two-dimensional maps of the [35S]methionine-labeled tryptic peptides of the mouse, hamster, and rat embryo proteins are similar to the maps of the corresponding proteins from SV40-transformed cells. Primary cells from midgestation mouse, hamster, or rat embryos contain one-third to one-half as much 55-kDal protein as a SV40-transformed mouse fibroblast cells and nearly the same amount as F9 mouse embryonal carcinoma cells. The amount of 55-kDal protein is greatly reduced on replating the mouse, rat, or hamster embryo primary cells. The amount of this protein in mouse embryos is dependent on the stage of the embryo. The embryo proteins are phosphoproteins. (Author abstract) (32 Refs)

42. TYROSYLPROTEIN KINASE AND PHOSPHATASE ACTIVITIES IN MEMBRANE VESICLES FROM NORMAL AND ROUS SARCOMA VIRUS-TRANSFORMED RAT CELLS.

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Proc Natl Acad Sci USA; 78(11,part2):6689-6693 1981

Membrane vesicles, isolated from normal and Rous sarcoma virus-transformed rat cells, have an associated cyclic-AMP independent kinase that phosphorylates a Mr 37,000 protein in vesicles from normal cells and proteins of Mr 37,000, 50,000, and 67,000 in vesicles from transformed cells. Proteins in vesicles from normal and transformed cells contain 9% and 77%, respectively, of their labeled phospho amino acids as phosphotyrosine. Thus, isolation of vesicles and subsequent incubation with [gamma-32P]ATP enriches the proportion of labeled phosphotyrosine in proteins (relative to other phospho amino acids) by two orders of magnitude over that found in intact cells. The in vitro phosphorylation of each of these proteins is enhanced in the presence of 10 uM Zn++, a phosphotyroslyprotein phosphatase inhibitor. From these studies it appears that membrane vesicles may be a valuable system for examination of transformation-specific phosphorylation of proteins. (Author abstract) (25 Refs)

43. NONLYTIC SIMIAN VIRUS 40-SPECIFIC 100K PHOSPHOPROTEIN IS ASSOCIATED WITH ANCHORAGE-INDEPENDENT GROWTH IN SIMIAN VIRUS 40-TRANSFORMED AND REVERTANT MOUSE CELL LINES.

Chen S, Verderame M, Lo A, Pollack R
Dept. Biological Sciences, Columbia Univ., New York, NY, 10027
Mol Cell Biol; 1(11):994-1006 1981

The two distinct growth controls of normal fibroblasts can be assayed as requirements for serum or anchorage. Interaction of mouse 3T3 fibroblasts with simian virus 40 (SV40) generates four lines of transformed (TR) cells (fully TR, anchorage TR, serum TR and fully reverted). Viral gene expression was studied in these four lines. Immunoprecipitation of (35S)methionine labeled cell extracts with an antiserum from tumor-bearing hamsters detected the SV40 large T and small t proteins (94,000 mol wt [94K], 17K) and the nonviral host 54K protein in all four lines. A 100K tumor antigen was found in some, but not all lines; similar molecules have been reported in many rodent transformed lines. Analysis of the relation of phenotype to relative amounts of the various proteins in the cell classes, using the Spearman rank correlation test, showed the amount of 100K T antigen relative to 94K T antigen or to total viral protein correlated well with ability to form colonies in semisolid medium. No significant correlation was found between quantities of labeled 94K T antigen, 54K host antigen, or 17K t antigen and either serum or anchorage independence. Mouse cell TR with small t SV40 deletion mutant 884 synthesized a 100K T antigen, suggesting small t is not required. The 100K T antigen migrated more slowly than the lytic T. It is concluded that since mixtures of extracts from cells expressing and lacking the 100K T antigen yielded the expected amount of this protein, it is unlikely that the 100K T derives from the 94K protein by a posttranslational modification. (70 Refs)

44. COMPARISON OF T ANTIGEN-ASSOCIATED HOST PHOSPHOPROTEINS FROM SV40-INFECTED AND -TRANSFORMED CELLS OF DIFFERENT SPECIES.

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J Gen Virol; 55(part2):367-378 1981

Simian virus 40 (SV40)-infected and -transformed cells contain, in addition to the virus-coded tumor antigens, one or more 48K to 56K host tumor antigens. At least part of this class of host proteins exists as a fast-sedimenting complex with the SV40 large T antigen. The host proteins associated with the large T antigen in SV40-transformed monkey, mouse and human cells and SV40-infected monkey cells were compared by two-dimensional gel electrophoresis and V8 partial proteolysis peptide mapping. Although these proteins differed slightly in apparent mol wt and peptide pattern, they migrated identically in isoelectric focusing gels. These results suggest that the cellular proteins associated with large T antigen in different hosts are very closely related to each other. Despite their similarities, the 55K proteins from different host cells form complexes of different stabilities with large T antigen, as judged by spontaneous dissociation of the complexes during storage, and the fractions of the 55K cellular protein and large T antigen found free and in the complexed form in each different host cell. (Author abstract) (36 Refs)

45. EVIDENCE THAT VIRAL TRANSFORMING GENE PRODUCTS AND EPIDERMAL GROWTH FACTOR STIMULATE PHOSPHORYLATION OF THE SAME CELLULAR PROTEIN WITH SIMILAR SPECIFICITY.

Erikson E, Shealy DJ, Erikson RL
Dept. Pathology, Univ. Colorado Sch. Medicine, Denver, CO, 80262
J Biol Chem; 256(22):11381-11384 1981

Treatment of A-431 human epidermoid carcinoma cells with epidermal growth factor (EGF) was shown to enhance the phosphorylation of a Mr = 34,000 protein. Because the phosphorylation of an analogous protein is enhanced in various cell lines transformed by Rous sarcoma virus (RSV) we characterized the phosphorylation of the A-431 Mr = 34,000 protein under these two conditions in order to determine whether there are common pathways between viral transformation and EGF stimulation. The results of tryptic phosphopeptide mapping and phosphoamino acid analysis showed that the Mr = 34,000 protein was phosphorylated in an identical manner by the EGF-stimulated protein kinase activity and by the protein kinase activity of the RSV transformation-specific protein or of its normal cell homolog. Although the specific protein kinase that phosphorylates the Mr = 34,000 protein under conditions of EGF-stimulation is not yet identified, these studies demonstrate that at least one consequence of EGF stimulation is identical with one of the consequences of viral transformation. (Author abstract) (43 Refs)

46. VIMENTIN-DERIVED PROTEINS: DIFFERENCES BETWEEN NORMAL HUMAN FIBROBLASTS AND TRANSFORMED HUMAN CELLS.

Ochs DC, McConkey EH, Guard NL
Dept. Molecular, Cellular and Developmental Biology, Univ. Colorado, Boulder, CO, 80309
Exp Cell Res; 135(2):355-362 1981

Two-dimensional gel electrophoresis revealed a quantitative difference in a series of polypeptides ranging in mol wt from 45,000 to 51,000 and of lower isoelectric pH than vimentin, when comparing normal human fibroblasts with a virally transformed subline and with HeLa cells. Re-extraction of purified [35S]vimentin with cold whole cell homogenates and peptide mapping showed that these polypeptides are derivatives of vimentin. They may be natural components of a normal fibroblast's architecture or they may arise from a pool of vimentin that is not structured within intermediate filaments at the time of extraction. Furthermore, we show that vimentin from the two transformed cell types is more resistant to proteolysis by whole cell homogenates that vimentin from normal fibroblasts. Structural alteration of vimentin may play an important role in the expression of transformation. (Author abstract) (14 Refs)

47. PATTERNS OF CYCLIC NUCLEOTIDES AND RELATED ENZYMES IN NORMAL AND GROSS-VIRUS-TRANSFORMED RAT THYMOCYTES.

Peracchi M, Lombardi L, Bamonti-Catena F, Maiolo AT, Polli EE
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Leuk Res; 5(4/5):413-420 1981

Cyclic nucleotide content and cyclase and phosphodiesterase activities in normal and Gross virus-transformed rat thymocytes were studied. Differences in cyclic nucleotide levels and in cyclase activities depended on how the data were expressed. Cyclic AMP (cAMP) levels were significantly lower in transformed than in normal thymocytes on the basis of protein content but no differences were apparent on the basis of cell number or DNA content. Cyclic guanosine monophosphate (cGMP) levels in transformed vs normal cells were also significantly reduced when the data were expressed per mg of protein, but significantly higher when based on cell number or DNA content. The cAMP/cGMP M ratio was 13.4 +-1.74 in transformed and 19.2 +-2.56 in normal thymocytes (p less than 0.02). Both adenylate cyclase and guanylate cyclase activities were significantly lower in transformed than in normal cells on the basis of protein content; no differences were apparent on the basis of cell number or DNA content. cAMP phosphodiesterase and cGMP phosphodiesterase activities, studied at two substrate concentrations (1 and 100 uM), were significantly higher in transformed than in normal thymocytes either per cell number, protein content, or DNA content. Normal thymocytes significantly increased cyclic nucleotide levels in response to isoproterenol, serotonin, carbamylcholine, sodium azide, and theophylline, but transformed thymocytes responded only to the latter two agents. The data indicated that cyclic nucleotide metabolism is abnormal in malignancy. (30 Refs)

48. DNA METHYLATION IN NORMAL AND SV40-TRANSFORMED HUMAN FIBROBLASTS.

Diala ES, Plent MM, Coalson DW, Hoffman RM
Dept. Pediatrics, M009, Univ. California at San Diego Sch. Medicine, La Jolla, CA, 92093
Biochem Biophys Res Commun; 102(4):1379-1384 1981

The results of high performance liquid chromatographic studies in four normal and four simian virus 40 (SV40)-transformed human diploid fibroblast cultures indicated that SV40 transformation does not affect the extent of total genomic DNA methylation in human fibroblasts. This is in contrast with the results of other studies, which suggest that transforming viruses do affect the extent of total genomic methylation. The possibility that SV40 transformation causes changes in site-specific DNA methylation in human cells remains to be investigated. (18 Refs)

49. ONCOGENIC TRANSFORMATION AND THE REDUCTIONS OF INSULIN SECRETION AND PROLIFERATIVE CALCIUM DEPENDENCE DURING REPEATED PASSAGE OF PANCREATIC ISLET CELLS IN VITRO.

Whitfield JF, Boynton AL, Healy GM, Sun AM
Animal and Cell Physiology Group, Natl. Res. Council Canada, Ottawa, Ontario K1A OR6, Canada
Cancer Lett; 14(2):159-168 1981

Changes in calcium-dependent ability to secrete insulin and proliferative calcium-dependence of fetal bovine pancreatic islet cells during passage through successive generations were analyzed. Although the insulin content of fetal pancreas did not change appreciably between passage 3 and 12, insulin secretion fell to non-detectable levels over this period. Proliferation of islet cells could be stopped or greatly lowered by reducing the calcium concentration from 1.8 to 0.02 milliM. However, as with insulin secretion, this sensitivity to extracellular calcium deprivation declined and eventually vanished as the cells passed through successive generations and their proliferative capacity increased. Reductions of insulin secretion and proliferative calcium dependence were accompanied by oncogenic transformation. (29 Refs)

50. ALTERATIONS IN GROWTH REQUIREMENTS OF KIDNEY EPITHELIAL CELLS IN DEFINED MEDIUM ASSOCIATED WITH MALIGNANT TRANSFORMATION.

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J Supramol Struct Cell Biochem; 15(1):63-72 1981

Association of changes in growth requirements of kidney epithelial cells with malignant transformation was studied. Madin Darby Canine Kidney (MDKC) and baby mouse kidney (BMK) cell lines were cultured on Medium K-1 (serum-free medium supplemented with insulin, transferrin, prostaglandin E1 (PGE1), triiodothyronine (T3), and hydrocortisone). Both cell types grew on K-1 and responded to the individual supplements. Deletion of any single supplement resulted in decreased culture growth. The fewest MDKC or BMK colonies were found if transferrin or PGE1 was deleted. Results indicated MDKC as a suitable model for normal kidney cells in vitro. Malignant transformation of MDKC by Moloney sarcoma virus resulted in reduction of the optimal dose of insulin and the elimination in some cells of the PGE1 requirement. Transformed cells required fibronectin for growth in K-1. Variant cells were tumorigenic in adult nude mice and had altered cyclic AMP metabolism. (20 Refs)

51. ALKALINE PHOSPHATASE ISOZYMES FROM RAT TRANSPLANTABLE GASTRIC CARCINOMA TISSUES INDUCED BY N-METHYL-N'-NITRO-N-NITROSOGUANIDINE (MEETING ABSTRACT).

Miki K, Kobori O, Ichinose M, Miyazaki J, Iino S, Niwa H, Suzuki H, Oka H, Oda T

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Oncodev Biol Med; AbstractsBook,1:P11 1981

Experimental gastric carcinoma was developed in inbred Wistar strain rats by oral administration of N-methyl-N'-nitro-N-nitrosoguanidine, and the resulting tumor was transplanted sc into rats of the same strain. Alkaline phosphatase (ALP) isozymes were determined in these transplantable tumor tissues, and their enzymological and immunological characterizations were analyzed. They did not differ significantly until the 19th generation, and were almost the same as those of primary tumors in out-bred rats; the carcinoma tissues of rat stomach were suspected of producing high amounts of ALP isozymes (major A -band and minor B-band), especially the intestinal-type ALP isozyme (B-band). Therefore, abnormal gene expression in ALP production, especially intestinal-type ALP, seemed to be independent of the strain of rats and inherited in transplantable tumor until the 19th generation. However, after the 20th generation, specific ALP activity gradually decreased and zymogram showed almost only A-band (non-intestinal-type ALP). We propose that experimentally induced rat gastric cancer cells, initially or precancerous condition, produce the A-type of ALP isozyme, finally, as cancer cells develop, they produce the B-type, and ultimately, A plus A-type isozyme appear in the carcinoma tissues. After the 20th generation, ALP isozymes from rat transplantable tumor tissue become similar to ALP isozymes of the precancerous condition. (2 Refs)

52. INTRACELLULAR CONTENT OF SODIUM AND OTHER ELEMENTS AS RELATED TO THE CONTROL OF PROLIFERATION OF NORMAL AND TRANSFORMED CELLS.

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Diss Abstr Int [B]; 42(3):881-B 1981

Significantly higher intracellular levels of Na were found in both the H6 hepatoma and the 13762 NF mammary adenocarcinoma as compared to their normal counterpart cells in vivo. Amiloride, a drug known to block passive Na+ influx, was shown to inhibit H6 hepatoma and DMA/J mammary adenocarcinoma growth in vivo and to inhibit H6 cell and DMA/J cell proliferation in vitro. Treatment of animals bearing an H6 hepatoma with amiloride caused a decrease in intracellular Na, but not in a dose-dependent manner. In fact, the group receiving the lowest dosage of amiloride had the lowest levels of intracellular Na, but tumor growth had not been significantly inhibited at that dosage. Thus, the intracellular level of Na was not directly related to tumor growth. This would suggest that high intracellular levels of Na are related to oncogenesis, but may be a result of the cancer lesion(s) rather than a cause. In accordance with current findings published in the literature, Na+/influx may play a greater role in the regulation of cell proliferation than does its intracellular concentration. Therefore, it may be that amiloride inhibited proliferation of the different cell types due to its inhibition of Na+ influx. (no Refs)

53. THE METABOLISM OF BENZO(A)PYRENE IN TRANSFORMABLE AND NONTRANSFORMABLE C3H MOUSE FIBROBLAST CELL LINES.

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Diss Abstr Int [B]; 42(3):913-B 1981

Incubation of benzo(a)pyrene (BaP) with intact C3H/10T1/2 cells for 48 hr resulted in the conversion of this carcinogen to organic-soluble derivatives, which cochromatographed with benzo(a)pyrene-7,8-dihydrodiol, benzo(a)pyrene-9,10-dihydrodiol, and 3-and 9-hydroxybenzo(a)pyrene, and to water -soluble derivatives. The metabolic activation of BaP was studied by testing a comprehensive series of 9 BaP metabolites for their ability to transform C3H/10T1/2 cells. Of all the derivatives examined, only (+/-) benzo(a)pyrene-7,8-dihydrodiol was as active as the parent hydrocarbon in the production of oncogenic transformation. In addition, the major DNA-binding species produced in BaP-treated C3H/10T1/2 cells was identified as benzo(a)pyrene-7,8-dihydrodiol-9,10-epoxide. These results strongly support current proposals that benzo(a)pyrene-7,8-dihydrodiol and benzo(a)pyrene-7,8-dihydrodiol-9,10-epoxide are the proximal and ultimate carcinogenic forms of BaP. The basis for cellular susceptibility to oncogenic transformation was investigated by comparing the metabolism of BaP by CVP3SC6 (CVP) cells, which are not responsive to BaP-induced transformation, and by C3H/10T1/2 cells. Although CVP cell microsomes were not as active as C3H/10T1/2 cell microsomes in the metabolism of BaP, its metabolism by intact CVP and C3H/10T1/2 cells was quantitatively and qualitatively very similar. CVP cells could be transformed by BaP treatment plus exposure to the tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA). CVP cells treated with BaP plus TPA exhibited both morphological alterations and a loss of anchorage dependence. These studies emphasize that not only metabolic activation leading to DNA adduct formation and mutagenesis, but also the ability to express carcinogen-induced damage play an important role in determining cellular susceptibility to carcinogenesis. (no Refs)

CELL SURFACE PHENOMENA OF TRANSFORMATION

54. SIMILARITIES AND DIFFERENCES BETWEEN THE FIBRONECTINS OF NORMAL AND TRANSFORMED HAMSTER CELLS.

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J Biol Chem; 256(22):11708-11715 1981

Fibronectins from normal and virally transformed hamster cells were compared by several criteria. The fibronectin from transformed cells was similar to that from normal cells in being an intact dimeric glycoprotein with the ability to bind to gelatin, activated thiol-Sepharose, and cells. No evidence was found for proteolytic cleavages or abnormalities in disulfide bonding of transformed cell fibronectin. This fibronectin was also shown to be active in promoting cell attachment, elongation, and alignment. Therefore, the fibronectin produced by transformed cells is not defective. However, it was shown that the transformed cells were partially deficient in their capacity to bind fibronectins from either normal or transformed cells. This deficiency has implications for the significance of the loss of fibronectin on oncogenic transformation. Partial proteolysis of the fibronectins from normal and transformed cells gave rise to the same fragments. However, the glycosylated fragments from transformed cell fibronectin appeared somewhat larger than those from normal cell fibronectin. Analysis of fibronectin glycopeptides showed that transformation leads both to more branches per core and to a higher sialylation of the asparagine-linked complex carbohydrate side chains. (Author abstract) (55 Refs)

55. GLYCOLIPIDS: RECEPTORS FOR FIBRONECTIN?

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J Cell Physiol; 109(2):343-351 1981

Three different assays of fibronectin biological activity were examined for their sensitivity to inhibition by glycolipids. These assays measured cell-cell or cell-substrate adhesive interactions, and quantitate fibronectin's hemagglutinating activity, capacity to mediate cell spreading on plastic dishes, and restoration of normal alignment and morphology to transformed cells. Gangliosides inhibited fibronectin-mediated hemagglutination, cell spreading, and restoration of a normal morphologic phenotype to transformed cells. Of the other lipids tested which were less effective inhibitors, the more negatively charged were the most effective. The most effective ganglioside inhibitors generally contained the most sialic acid residues. The oligosaccharide portions of gangliosides retained inhibitory activity; those with more sialic acid were more effective. These results are consistent with the notion that the 'receptor' for fibronectin on a variety of cell types contains a negatively charged lipid, eg, a ganglioside. Lipids other than gangliosides could conceivably serve as ligands for fibronectin interaction, depending on their concentration on the cell surface. The specificity for certain gangliosides is relative rather than absolute. There is no evidence that fibronectin needs a living cell for its ganglioside-inhibitable activity. Oligosaccharides on glycoproteins may not be fibronectin receptors, since purified glycopeptides did not inhibit hemagglutination. (32 Refs)

56. PATTERNS OF CELL COMMUNICATION AND DIFFERENTIATION IN SV40 TRANSFORMED HUMAN KERATINOCYTES.

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J Cell Physiol; 109(1):153-159 1981

The effect of viral transformation on intercellular communication (IC) and cellular differentiation in human keratinocytes was studied. Human keratinocytes from neonatal foreskin were grown on lethally irradiated 3T3 feeder cell layers. Uninfected cultures were compared with cultures infected with the oncogenic virus SV40. IC was studied by microinjection of fluorescein. Cell maturation was determined by cytochemical staining. Uninfected keratinocytes showed extensive coupling, as indicated by widespread exchange of fluorescein. No communication with mouse feeder cells or human fibroblasts was noted. The effects of SV40 infection appeared after three to four serial passages, when 50-70% of the cells were T-antigen positive. IC was apparent only within small groups of cells. Maturation of uninfected cells was loosely dependent on cell colony size. Keratinizing cells in infected cultures appeared only after formation of confluent sheets, indicating that SV40 infection greatly increases the cell density-dependence of keratinocyte maturation. The results are consistent with a requirement of IC for differentiation of keratinocytes. (20 Refs)

57. CORRELATION BETWEEN MEMBRANE PERMEABILITY AND INDUCTION OF ERYTHROID DIFFERENTIATION BY DMSO IN FRIEND VIRUS TRANSFORMED ERYTHROLEUKEMIA CELLS (MEETING ABSTRACT).

Dube SK, Yamane T
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

How erythroid differentiation is blocked by the Friend virus complex (FVC) or how it is induced by dimethylsulfoxide (DMSO) and other chemicals is not clear. One possibility is that transformation by the FVC leads to an effect on the proerythroblast membrane in such a way that it becomes more permeable to small nutrient molecules and the transformed proerythroblasts thus acquire a proliferative advantage. A prediction of this model would be that DMSO and other inducers reverse this effect. We have measured the uptake of phosphate, leucine, uridine, thymidine and deoxyglucose by Friend erythroleukemic (FEL) cells before and after induction with DMSO. The results showed a dramatic decrease in the uptake of these molecules by induced cells amounting to a drop of about 70% of the control. Our experiments on 32P phosphate incorporation in these cells showed that newly synthesized globin messenger RNA (mRNA) appears in the cytoplasm about 10 hr after addition of DMSO. To determine whether the decrease in membrane permeability temporally coincided with globin mRNA induction, we measured the uptake of phosphate, leucine, etc at hourly intervals after addition of DMSO. A very interesting duality of effect was observed. At first hr time point, there was an increase in the uptake of these molecules and this increase continued up to about 8 hr. After that time the uptake showed first signs of decrease and this was almost concomitant to the initiation of induced globin mRNA synthesis. To further strengthen the interpretation of the uptake data, we used amphotericin B, which is known to increase membrane permeability. We found that if amphotericin B and DMSO are added together, the inducing effect of DMSO is totally wiped out, ie, no globin synthesis is observed. These results, therefore, strongly argue for a correlation between decrease in membrane permeability and induction of erythroid differentiation in FVC transformed proerythroblasts. (no Refs)

58. A TUMOR-SPECIFIC MEMBRANE PHOSPHOPROTEIN MARKER IN HUMAN CELL HYBRIDS.

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Dept. Microbiology, Coll. Medicine, Univ. California, Irvine, CA, 92717
Cell; 26(3,part1):429-438 1981

Fusion of normal human fibroblasts with HeLa results in hybrids with completely suppressed tumorigenic potential, which still behave as transformed cells in culture. From these stably suppressed hybrids, rare tumorigenic segregants have been isolated. We prepared antiserum against one tumorigenic segregant, ESH5T, by injecting live cells into rabbits, then absorbed this antiserum extensively against the corresponding nontumorigenic hybrid, ESH5, to remove any cross-reacting antigenic specificities. Immunoprecipitation of iodinated cell surface proteins with this absorbed antiserum revealed a 75 kilodalton (kd) protein on the cell surface of tumorigenic HeLa-fibroblast hybrids and HeLa, but not on normal fibroblasts or any nontumorigenic hybrids examined. Under nonreducing conditions in SDS-polyacrylamide gel electrophoresis the 75 kd protein migrated as a 150 kd dimer. Immunoprecipitation of cells metabolically labeled with 35S-methionine confirmed that the 75 kd protein is synthesized in tumorigenic cells but not in nontumorigenic hybrids or normal fibroblasts. Metabolic labeling withe 32PO4 revealed that the 75 kd protein is phosphorylated, and immunoprecipitation of galactose-oxidase/3NaBH4-labeled cells with absorbed antiserum identified it as a glycoprotein. This protein does not appear to be a major cell surface iodination component and represents only 0.03% of the total cellular protein. The exclusive correlation of the expression of this cell surface phosphoglycoprotein with tumorigenicity in HeLa-fibroblast hybrids suggests that it may be an important determinant for in vivo growth potential. (Author abstract) (49 Refs)

59. LIVER CELL MEMBRANE ALLOANTIGENS AS CELLULAR MARKERS IN GENOTYPIC MOSAIC RAT LIVERS UNDERGOING CHEMICALLY INDUCED HEPATOCARCINOGENESIS.

Hunt JM, Buckley MT, Onnink PA, Rolfe PB, Laishes BA
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Cancer Res; 42(1):227-236 1982

We have developed a new marker system utilizing rat alloantigens as genetic cellular markers for hepatocytes in genotypic mosaic livers of rats undergoing hepatocarcinogenesis. This marker system has been designed to facilitate the eventual purification of subpopulations of hepatocytes from such livers which contain precursor cells of carcinomas. Thus, a lineage relationship between cells of early putative premalignant liver lesions and those of carcinomas may ultimately be established, and the process of cancer development may be biochemically probed. A donor-to-host liver cell transplantation procedure was used. Host rats subjected to a 2-acetylaminofluorene/partial hepatectomy regimen were grafted orthotopically iv with donor liver cells via a mesenteric vein of the hepatic portal system. Cryostat sections of host rat livers were prepared 10 to 13 days after donor liver cell transplantation for histochemical localization of gamma-glutamyltranspeptidase-positive (GT+) hepatocyte colonies Genotypic mosaic host rat livers were further analyzed by indirect immunofluorescence in serial cryostat sections to identify hepatocyte colonies on the basis of their strain-specific alloantigens. Polyvalent F344 anti-WF alloantiserum was prepared by immunizing F344 rats with WF skin and spleen cells. The resulting serum reacted positively by indirect immunofluorescence with cryostat liver sections as well as collagenase-dissociated hepatocytes from WF and WF x F344F1 hybrid rats. No reaction of the alloantiserum with F344 liver tissue or isolated hepatocytes was observed. Some F344 donor origin colonies did not express the GT+ phenotype and were classified as gamma-glutamyltranspeptidase-negative. With the aid of tissue architectural landmarks, 276 individual colonies were analyzed. Ninety-seven per cent of the colonies appeared to be of F344 donor origin (92% FA- GT+; 5% FA- gamma-glutamyltranspeptidase-negative); 3% were FA+ GT+; and apparently of F1 hybrid host origin. Rat alloantigens expressed on the surface of hepatocytes may offer the potential for purification of donor-origin putative premalignant hepatocytes from genotypic mosaic host rat livers at sequential stages of hepatocarcinogenesis. (31 Refs)

60. CELL SURFACE T ANTIGEN IN CELLS INFECTED WITH SIMIAN VIRUS 40 OR AN ADENOVIRUS-SIMIAN VIRUS 40 HYBRID, AD2+D2.

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J Virol; 40(2):615-619 1981

Cell surface T antigen, detected by a radioimmune assay that uses 125I-labeled Staphylococcus aureus protein A and antibodies against either authentic T antigen or D2 hybrid T antigen, was found in simian virus 40-transformed and -infected cells and in cells infected with an adenovirus-simian virus 40 hybrid, Ad2+D2. In simian virus 40 lytic infection, the surface T antigen appeared at the same time as the nuclear T antigen. (Author abstract) (22 Refs)

61. MEMBRANE GLYCOPEPTIDES FROM CHEMICALLY TRANSFORMED CELLS: COMPARISON BETWEEN MESENCHYMAL AND EPITHELIAL CELL LINES DERIVED FROM DIMETHYLNITROSAMINE-TREATED RAT KIDNEY.

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Cancer Res; 42(1):39-43 1982

The membrane glycopeptides of normal and chemically transformed malignant cell lines derived from rat kidney were investigated by gel permeation chromatography. The cell lines, which were metabolically labeled with L-[5,6-3H]fucose or D-[6-3H]glucosamine, were derived from rats treated in vivo with a carcinogenic dose of dimethylnitrosamine to induce both mesenchymal and cortical epithelial tumors in the rat kidney. Among the cell lines examined were: (a) transformed lines of mesenchymal type derived from the rat kidney 2 to 24hr after the dose of carcinogen; (b) mesenchymal tumor cell lines obtained from the dimethylnitrosamine-induced mesenchymal tumors occurring at 7 to 10 mo; (c) a transformed epithelial cell line derived from rat kidney 48 hr after the carcinogenic dose; and (d) an epithelial cell line obtained from a renal adenocarcinoma induced at 10 mo by a dose of diethylnitrosamine. For control comparisons, populations of normal renal epithelium and mesenchyme were cultured selectively from untreated rats. The radioactive glycopeptides of the neoplastic epithelial cell lines (transformed and tumor) displayed a shift to more complex higher-mol-wt glycopeptides when compared with the normal epithelial counterparts. These results were similar to those reported previously for other cell types. In contrast, the neoplastic cell lines of mesenchymal origin lacked higher-mol-wt glycopeptides, displaying patterns that were identical with those of normal renal mesenchymal cells. It is suggested from these results that the membrane glycopeptide alterations characteristic of virus-transformed and other tumor cells are not detected by these techniques in all cell lines transformed by chemical agents. Furthermore, cell lineage within the same organ may play a role in the observed difference. (Author abstract) (22 Refs)

62. RELATIONSHIP OF THE FELINE ONCORNAVIRUS ASSOCIATED CELL MEMBRANE ANTIGEN TO A FELINE SARCOMA VIRUS ENCODED POLYPROTEIN.

Snyder HW, Dutta-Choudhury M, Hardy Jr WD
No affiliation given
Haematol Blood Transfus; 26:488-491 1981

Using immunoaffinity chromatography on a column of Sepharose containing bound IgG from cat anti-feline oncornavirus-associated cell membrane antigen (FOCMA) serum, a 70,000-dalton protein was isolated from lysates of mink cells transformed by the Gardner-Arnstein strain of feline sarcoma virus (GA-FeSV). This result was unanticipated because previous evidence had suggested that FOCMA was associated with the much larger (95,000 dalton) gag-x fusion protein in these cells. The GA-FeSV gag-x protein was also isolated by virtue of its binding to anti-FeSV antibodies on a different affinity column. Preliminary biochemical characterization of the 70,000-dalton protein from both GA-FeSV-transformed mink fibroblasts and feline lymphosarcoma cells showed no differences between them. The gag-x protein was distinguishable by labelling with 32P-orthophosphate, association with protein kinase activity, and its precipitation ability with antibodies in a hyperimmune antiserum to FeLV structural proteins. It is hypothe sized that FOCMA may actually be a family of antigens, not all of which cross-react with FeSV polyprotein antigens. (21 Refs)

63. GLYCOPEPTIDES PREPARED FROM MOUSE CEREBRUM INHIBIT PROTEIN SYNTHESIS AND CELL DIVISION IN BABY HAMSTER KIDNEY CELLS, BUT NOT IN THEIR POLYOMA VIRUS-TRANSFORMED ANALOGS.

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Exp Cell Res; 136(1):31-41 1981

Glycopeptides isolated from mouse cerebral cortex cell surfaces (BCSG) were shown to inhibit cell growth and protein synthesis in baby hamster kidney (BHK)-21 cells, whereas polyoma virus-transformed BHK-21 cells (pyBHK-21) were refractory to the inhibitory activity of the glycopeptides. Growth inhibition was shown to be reversible and non-lethal to BHK-21 cells. Despite that difference in sensitivity to the action of the glycopeptides, both cell lines could bind the inhibitor in a saturable fashion and in similar quantities. After trypsinization, BHK-21 cells appeared refractory to the inhibitor, whereas pyBHK-21 cells became sensitive. The data suggested the presence of a receptor for BCSG on the cell surface of both cell lines. Incubating BCSG with conditioned medium from pyBHK-21 cells resulted in loss of the glycopeptide's inhibitory activity. In contrast, medium conditioned by BHK-21 cells had no effect on the inhibitory activity of BCSG. We hypothesize that the refractoriness of pyBHK-21 cells to BCSG is related to their autonomous growth characteristics and failure to respond to topo-inhibitory growth control. BCSG may be a naturally occurring growth regulatory whose function can be explored by use of the BHK-21/pyBHK-21 model system. (Author abstract) (34 Refs)

64. COMPARISON OF CELL SURFACE ANTIGENS EXPRESSED ON BLV-TRANSFORMED AND BOVINE LYMPHOSARCOMA CELLS (MEETING ABSTRACT).

Onuma M, Suneya M, Mikami T, Izawa H

No affiliation given

Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

In this paper we will describe the comparison of cell surface antigens among bovine leukemia virus (BLV)-transformed cells, adult lymphosarcoma (ALS) cells and skin lymphosarcoma (SLS) cells by complement-dependent antibody cytotoxicity (CDAC) test. To detect the similar antigen which is different from BLV structural proteins on ALS cells, seven individual ALS cells were tested. Five sera from cattle with ALS had BLV antibody, however only one serum (number 158) had cytotoxic antibody against seven individual ALS cells but not against SF-28 cells. None of the other 4 sera had cytotoxic activity against these 7 ALS cells and SF-28 cells. Serum from S-28 sheep did not have any cytotoxic activity against these ALS cells but had activity against the SF-28 cells. Absorption of the sera from number 158 and S-2 8 with purified BLV or normal bovine lymphoid cells could not remove the positive reaction against ALS and SF-28 cells, respectively. These results suggested that the major antigens expressed on ALS and SF-28 cells might differ from each other and from the BLV structural proteins. To compare the cell surface antigens between ALS and SLS cells, these 7 individual ALS cells and transplantable SLS cells in nude mice were used as target cells for CDAC test. None of the 5 sera from cattle with ALS and S-28 serum had cytotoxic activity against SLS cells. Sera from cattle with SLS, CLS and TLS did not have any cytotoxic activity against ALS, SLS, SF-28 and FLK cells. Serum from sheep (S-22) experimentally inoculated with SLS had cytotoxic activity against SLS cells but not against ALS, SF-28 and FLK cells. These results suggested that SLS cell may express specific antigen which differed from that of ALS, SF-28 and FLK cells. Comparison of the major cell surface antigens among FLK, SF-28, ALS and SLS cells showed that these cells expressed different antigens. Since the antigens expressed on SF-28, ALS and SLS cells were antigenically different from BLV structural proteins, they might be associated with neoplastic transformation such as tumor-associated cell surface antigen. (no Refs)

65. RECEPTOR MEDIATED LEUKEMOGENESIS (MEETING ABSTRACT).

Weissman IL, McGrath MS, Jerabek L
Stanford University, Stanford, CA
Exp Hematol; 9(Suppl9):120 1981

We have proposed an unusual hypothesis for a mechanism by which slowly transforming retroviruses might cause T and B cell leukemia: such viruses bear on their surface envelope glycoprotein. We propose that these retroviruses bind via their envelopes to antigen specific receptors on T and B cells, trigger proliferation of these cells in much the same way that antigen binding to normal T and B lymphocytes trigger proliferation, and infect these cells in a way that leads to continued production of antigen by receptor bearing lymphocytes. This could lead to unlimited proliferation by these cells in response to the antigen they produce. In this case the viral oncogene would be the gene coding for the envelope glycoprotein. We have demonstrated that each cloned T and B lymphoma indeed bears on its surface receptors specific for particular virus which is produced by them. Interruption of receptor binding to lymphoma cells prevents their further proliferation, and this usually can be reversed by addition of high concentrations of the specific binding virus. These receptors are present in vivo on T lymphoma cells and not on the surrounding thymocytes which predominate in the preleukemic period. Current work implicates the receptor molecules on B cell lymphomas to be either their surface immunoglobulins, or molecules which preferentially associate with such surface immunoglobulin. (no Refs)

MORPHOLOGICAL AND OTHER BIOLOGICAL ASPECTS OF ONCOGENIC TRANSFORMATION

66. ASSOCIATION OF MICROTUBULES AND INTERMEDIATE FILAMENTS IN NORMAL FIBROBLASTS AND ITS DISRUPTION UPON TRANSFORMATION BY A TEMPERATURE-SENSITIVE MUTANT OF ROUS SARCOMA VIRUS.

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Dept. Biochemistry, Univ. Western Ontario, London, Ontario, Canada N6A 5C1
Proc Natl Acad Sci USA; 78(11,part2):6986-6990 1981

By double indirect immunofluorescence, using primary rabbit antibodies to tubulin and guinea pig antibodies to vimentin, we have simultaneously labeled microtubules and intermediate filaments in several types of cultured normal fibroblasts. With well-spread interphase cells there was an extensive but not complete correspondence of the labeling patterns for the two filamentous structures out to the cell periphery. This correspondence existed both at a gross level, where parallel but not coincident arrays of thickly labeled strands of the two types of filaments were observed, and at a fine level, where thinly labeled strands of the two were superimposed. The results suggest that there may be some type(s) of molecular linkages between microtubules and vimentin intermediate filaments that is under metabolic control. With NRK fibroblasts infected with a temperature-sensitive mutant (LA23) of Rous sarcoma virus, cells grown at the nonpermissive temperature (3° C) showed the correspondence of the distributions of the microtubules and intermediate filaments characteristic of the normal phenotype but within 1 hr after a shift to the permissive temperature (33 C) there was an extensive retraction of the intermediate filaments around the cell nucleus whereas the microtubules remained dispersed into the cell periphery. These results suggest that one of the functions carried out by p60src, the protein kinase responsible for transformation by Rous sarcoma virus, may be to modify the component(s) involved in the putative linkages between microtubules and intermediate filaments in the normal cells. (Author abstract) (26 Refs)

67. CORRELATION OF IN VITRO PROPERTIES AND TUMOURIGENICITY OF HAMSTER KIDNEY CELLS TRANSFORMED BY BK VIRUS.

Possati L, De Luca S, Ciarallo G, Portolani M
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J Gen Virol; 55(part2):481-486 1981

Hamster kidney cells transformed by BK virus (HKBK cells) were studied at low passage (about 30 subcultures) after transformation and at high passage (about 130 subcultures) after transforming. Several in vitro properties (rescue of virus, presence of T antigen, colony formation on plastic, in soft agar, on monolayers of normal cells, and serum dependency of growth) and tumorigenicity of these cells for newborn and adult hamsters were compared. HKBK cells at low passage showed high levels of T antigen, the growth properties of normal cells and low tumor-producing ability, while HKBK cells at high passage showed low levels of T antigen, the growth properties of transformed cells and high tumor-producing ability. These results may indicate that cellular transformation by BK virus is initiated, but not maintained, by the expression of genes regulating T antigen, and that the maintenance of the transformed state is due to complicated cellular and viral gene interactions occurring during the course of cell life. (Author abstract) (18 Refs)

68. KARYOTYPES AND CELL PHENOTYPES IN ACUTE LEUKEMIA FOLLOWING OTHER DISEASES.

Berger R, Bernheim A, Daniel MT, Valensi F, Flandrin G, Brecher G, Van Bekkum DW, Bernard J, Breton-Gorius J, Dreyfus B, McCulloch EA
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Blood Cells; 7(2):293-299 1981

Analysis for cytological and cytogenetic characteristics of acute lymphoblastic leukemias following other blood diseases or exposure to carcinogens revealed that some secondary acute leukemias were unclassifiable in the FAB (French, American, British) system. Monosomy 7 was associated with megakaryocyte abnormalities. These cytological and cytogenetic variations were studied in pooled samples from patients with acute nonlymphocytic leukemia and in similar patients following polycythemia vera. (8 Refs)

69. THE ROLE OF CHROMOSOME 15 IN MURINE LEUKEMOGENESIS. I. CONTRASTING BEHAVIOR OF THE TUMOR VS. NORMAL PARENT-DERIVED CHROMOSOMES NO. 15 IN SOMATIC HYBRIDS OF VARYING TUMORIGENICITY.

Spira J, Wiener F, Babonits M, Gamble J, Miller J, Klein G
Dept. Tumor Biology, Karolinska Inst., S-104 01 Stockholm, Sweden
Int J Cancer; 28(6):785-798 1981

G-banding analysis was carried out on a series of hybrids derived from the fusion of a chromosome 15-trisomic murine T-cell leukemia of AKR origin and normal diploid fibroblasts or lymphocytes of the CBT6T6 strain. Due to the 14;15 translocation involved in the generation of the T6 marker, the chromosomes No 15 and 14 derived from the normal and the tumor parent can be distinguished cytogenetically. Highly tumorigenic, in vitro maintained hybrids, and high-tumorigenic segregants of originally low-tumorigenic in vitro hybrids, selected by in vivo passage, showed a similar cytogenetic pattern. It was characterized by the amplification of the tumor-derived chromosome No 15 from the expected 3 to 5.5 +-0.2 copies and a concomitant decrease of the normal derived T(14;15)6 from two copies to 0.9 +-0.2. All other autosomes except No 14 showed only minor random variations, around the expected number of four copies. The tumor-derived chromosome 14 was amplified from the expected two to three copies. The low-tumorigenic hybrids showed the opposite pattern with a decrease in the number of the tumor-derived 15 chromosome from 3 to 2.6 +-0.1 and the maintenance of the two normal parent derived T(14;15)6 chromosomes. These findings suggest the existence of a qualitative difference between the 15 chromosomes derived from the tumor vs the normal parent, due to mutation or proviral DNA insertion in the tumor-derived homologue. Amplification of the changed locus and a decrease in the dosage of its normal counterpart appear to favor tumorigenicity. (Author abstract) (20 Refs)

70. SPONTANEOUS AND INDUCED HERPESVIRUS GENOME EXPRESSION IN MAREK'S DISEASE TUMOR CELL LINES.

Calnek BW, Shek WR, Schat KA

Dept. Avian and Aquatic Animal Medicine, New York State Coll. Veterinary Medicine, Cornell Univ., Ithaca, NY, 14853

Infect Immun; 34(2):483-491 1981

We incubated 31 newly established Marek's disease tumor cell lines at 41 C for 48 hr after subculturing and then examined them to determine the spontaneous rates of expression of viral internal antigen(s), viral membrane antigen(s), and virus isolation. All but two of the lines were isolated from tumors induced by clone-purified Marek's disease virus strains JM-10, GA-5, RB-1B, and BC-1A in nine different genetic strains of chickens with defined histocompatibility antigens. The line-to-line variations in the rates of spontaneous expression for the antigens or virus rescue were great, but the levels of expression were very low in most cases. The median rates of expression for viral internal antigen, viral membrane antigen, and virus isolation were 32, 8, and 2 positive cells per 10(5) cells, respectively (ranges, 0 to 20,280, 0 to 22,990, and 0 to 220 positive cells per 10(5) cells, respectively). The ratio of viral internal antigen expression to virus isolation was extremely variable and often high, whereas the ratio of viral internal antigen to viral membrane antigen expression was more consistent and generally low. The virus strain which induced the cell line influenced the level of virus genome expression, but the cell genotype did not. Cell lines transformed by JM-10 virus, which exhibited low oncogenicity, had significantly (p less than 0.01) higher rates of expression than cell lines transformed by GA-5 and RB-1B viruses, which exhibited high oncogenicity. Treatment with iododeoxyuridine or incubation at 37 C induced increased rates of expression in most lines but not in all lines. The degree of enhanced expression was inversely proportional to the rate of spontaneous expression. (Author abstract) (32 Refs)

71. MYELOPROLIFERATIVE SARCOMA VIRUS (MPSV), A NEW TOOL FOR THE STUDY OF HEMATOPOIESIS.

Le Bousse-Kerdiles MC, Jasmin C, Smadja-Joffe F, Klein B, Pragnell I, Ostertag W, Cronkite EP, Brecher G, Lajtha L, Bessis M, McCullogh EA, Bernard J, Van Bekkum DW, Moore MA, Sachs L, Varet B

Dept ,Virology, Inst. Cancerology and Immunogenetics (INSERM U 50), 14/16, avenu e Paul Vaillant Couturier, 94800 Villejuif, France

Blood Cells; 7(1):105-123 1981

Data supporting the hypothesis that myeloproliferative sarcoma virus (MPSV) is capable of transforming hemopoietic stem cells are presented: a direct involvement of the stem cell population is indicated by the large increase in stem cell concentration in infected mice; indirect evidence from in vivo and in vitro experiments shows a partial independence of growth factors by two cell populations and may indicate that they are both derived from stem cells altered by MPSV. MPSV may be a new tool for studying the regulation of murine hemopoiesis and viral genetic information. (49 Refs)

72. INTERACTION OF SERUM AND CELL SPREADING AFFECTS THE GROWTH OF NEOPLASTIC AND NON-NEOPLASTIC FIBROBLASTS.

Tucker RW, Butterfield CE, Folkman J

Cell Proliferation Lab., Johns Hopkins Oncology Center, Baltimore, MD, 21205

J Supramol Struct Cell Biochem; 15(1):29-40 1981

The effects of variations in serum concentration and cell spreading on the growth of neoplastic and non-neoplastic cells was studied. Cell cultures of murine non-neoplastic 3T3 and simian virus 40 (SV40)-transformed 3T3 cells, Chinese hamster embryo non-neoplastic CHEF 18-1 and neoplastic CHEF 16-2, cells and human fibrosarcoma HT1080 cells were tested. Cell spreading was controlled with films of poly(2-hydroxyethyl methacrylate) in concentrations of 10(-2)-10(-4) dilutions. Cell numbers grew in proportion to cell spreading in both neoplastic and non-neoplastic cultures. Maintenance of cell rounding inhibited growth of non-neoplastic cultures, but not of neoplastic cultures. Net cell numbers did not increase in some neoplastic cultures when serum concentrations were increased above 10% with increased cell spread. All non-neoplastic cultures showed increased growth with increasing serum concentrations as they converted to the spread form. Sensitivity of normal cells to humoral factors evidently is controlled by cell form (spreading). This control is less evident in at least some neoplastic cells. (20 Refs)

73. THE ROLE OF CHROMOSOME ABERRATIONS IN HUMAN CANCER (MEETING ABSTRACT).

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Teach-In on Research Methods in Cancer, June 30, 1981, London, England Marie Curie Memorial Foundation; 1981

Numerous attempts to elucidate the role of chromosomal changes in carcinogenesis have been made recently and this has been due mainly to the improvement of cytological techniques. The involvement of chromosomes in neoplastic growth, is a natural outcome of Boveri hypothesis which suggested in a more definite form that malignancy was due to an abnormal chromosome content of the cells. The reputed Boveri's Chromosome theory of cancer, suggests that chromosomal aberration is the common pathway through which carcinogenic factors induce cancer. Certain types of cancer, especially the leukemias, are known to occur with a higher frequency in

Down's syndrome, in patients with sex chromosome anomalies and in their relatives. The anomalies may predispose these patients directly or indirectly to cancer and, furthermore, is not restricted only to patients with Down's syndrome or sex chromosmoe abnormalities. Certain diseases, considered to be preleukemic conditions, in addition to being carried by a recessive gene, show congenital chromosomal damage and finally develop into leukemia. In another inherited disease, Xeroderma Pigmentosa, the chromosomal aberrations present may be asynchrony of a particular chromosome during the mitotic cycle and could lead to aneuploidy and subsequent malignant transformation. Chromosomal studies and evaluation of mutagenic potential of all new and established drugs, food additives and environmental chemicals should be integral aspects of the current practices of safety evaluation of these substances, and the same stringent principles should be applied to the numerous chemicals used as solvents and intermediates in industrial processes. Persons exposed to high risk, such as those working in chemical industries, must be monitored constantly using all the methodologies at hand. (no Refs)

74. CYTOGENETIC CORRELATES OF LEUKEMOGENESIS IN RATS: SHORT- AND LONG-TERM EFFECTS OF 7,12-DIMETHYLBENZ(A)ANTHRACENE ON CHROMOSOME BANDING.

Wolfe RN
University of Kentucky, Lexington, KY, 40506
Diss Abstr Int [B]; 42(4):1313-B 1981

The hypothesis tested in this dissertation is that a correlation exists between the vulnerable chromosome sites of acute damage induced in marrow cell chromosomes by the carcinogen 7,12-dimethylbenz(a)anthracene (DMBA) and the pattern of altered chromosomes found in the marrow cells of rats made leukemic by DMBA. Chromosome banding techniques which permit identification of the individual rat chromosomes were instituted for this study. The location of chromosome alterations can be specified with regard to bands, sub-bands and banding regions. In short-term (acute) experiments, DMBA induced in high incidence of chromosome breaks. On banded chromosomes, breaks were distinguished from light bands only when chromosomes were stained sufficiently dark or when banding on sister chromatids was not aligned. Some chromatid breaks appeared to be intercalary deletions; other breaks appear to be without deletion (loss of substance) but with the chromosome axis malaligned. Breaks in the terminal regions were common. The chromatid breaks induced by DMBA were shown to be nonrandom and were highest in chromosome regions 2q2, 6q2, 1p1, 1q3, 5q3, 4q2, 6q1, and 12p1. These data indicated that the damage induced by DMBA is nonrandom, some chromosome regions showed greater vulnerability to damage by DMBA. Markers chromosomes in leukemic marrow cells in volved t(1;2); t(1;4); t(1;6); t(1;7); t(1;9), with each associated with one normal chromosome 1 (monosomy 1p) and two normal number 2, No 4, No 6, No 7, or No 9 chromosomes. Trisomy No 2, 16 and 20 and monosomy No 5, 6, 10 and 18 occurred in leukemic rats but not in control rats. The data presented suggest that leukemogenesis by DMBA requires specific changes at multiple (ie, combination) chromosome sites. The number of these postulated critical sites required in the combination is not known, but our data identify the following morphologic regions as likely to contain these sites: 1q2, q3; the pericentromeric region of No 2 chromosome; 4q4; 5q3; 6q1; 6q2; 9q3; 11p; 12p; and 12q1. (no Refs)

75. CYTOGENETEIC ANALYSIS OF HUMAN MALIGNANT MELANOMA CELL LINES. RELATION TO TUMORIGENICITY IN NUDE MICE (MEETING ABSTRACT).

Bertrand S, Jacubovich R, Cabrillat H, Leftheriotis E, Dore JF
INSERM U218, Lyon, France
Third European Workshop on Melanin Pigmentation, September 28-October 1, 1981, Prague, Czechoslovakia. Czechoslovak Medical Society 128 pp., 1981.

On 36 cell lines, derived from human melanomas and obtained from 31 patients, karyotype analyses, utilizing banding techniques were carried out. Gross aneuploidy was seen in all mitoses. Majority of cell lines had modal distribution near triploidy. All cell lines derived from different individuals were identifiable by their marker chromosomes. When multiple cell lines were derived from a single biopsy specimen or from two different lesions of the same patient, common marker chromosomes were always observed. Markers, common to all of the mitoses of a given cell line, were identifiable over several mo or yr in culture, thus denoting stability of these markers. Interesting features appeared when the cytogenetic studies of 10 melanoma lines were compared to their ability to grow in athymic nude mice. We determined the number of copies of normal chromosomes and their involvement in the constitution of markers. Highly tumorigenic cell lines had majority of their mitoses characterized by either numerous copies or (and) involvement of chromosomes 3, 7, 16, 22 in the constitution of markers and relatively few copies of chromosome 9. On the contrary poorly tumorigenic cell lines had majority of their mitosis characterized by either few copies or relatively infrequent involvement of chromosomes 3, 7, 16, 22 in the constitution of markers, but a relatively high number of chromosome 9. Cell lines with intermediate tumorigenicity were shown to contain several subpopulations characterized by mitoses containing either numerous or few copies of chromosomes 3, 7, 16, 22 and 9. (no Refs)

76. GENETIC RESTRICTION (FV-1 AND FV-2) OF IN VITRO ERYTHROID TRANSFORMATION BY FRIEND POLYCYTHEMIA VIRUS (FVP). (MEETING ABSTRACT).

Hankins WD, Luna J
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. The Association 187 pp., 1981.

An in vitro transformation system which may be useful in elucidating the mechanism by which FVP causes erythroleukemia in mice has recently been described. Using this in vitro system, we have examined two genetic loci, Fv-1 and Fv-2, which are responsible for resistance to the in vivo effects of FVP in certain strains of mice. Different genetic stocks containing identical spleen Focusing Forming Viruses (SFFV) were prepared by superinfecting an SFFV nonproducer clone with either B-tropic or NB-tropic helper Murine leukemia Viruses (MuLV). The B- and NB-tropic pseudotypes produced by the superinfected cells were tested for their ability to transform marrow cells from Balb/c (Fv-1b, Fv-2s), DBA2 (Fv-1n, Fv-2s), Balb x DBA F1 hybrids, and C57/Bl (Fv-1b, Fv-2r). N- and NB-tropic infectious plasma preparations were also tested. N- and B-tropic viruses induced the development of erythroid bursts only in N-type (DBA/2) and B-type (Balb/c) marrow, respectively. Neither virus preparation was active in the Balb x DBA F1 hybrid marrow. On the other hand, the NB-tropic stocks were active on marrow from DBA/2, Balb/c, and the hybrids. None of 4 virus preparations induced erythroid burst formation in C57/B1 marrow. Mixing experiments (resistant and susceptible marrows) indicated the Fv-2 restriction was intracellular rather than intercellular. Control studies with the hormone, erythropoietin, demonstrated that the C57/B1 marrow was erythropoietically active in vitro. These results demonstrate that FVP-induce erythroid burst transfomation is under genetic control at the Fv-1 and Fv-2 loci and provide a system for an in vitro analysis of the genetic restrictions. (1 Ref)

77. TUMOR ASSOCIATED MORPHOLOGICAL MARKERS (MEETING ABSTRACT).

Nieburgs HE
Department of Pathology, Mount Sinai School of Medicine of The City University of New York, New York, NY
Twenty-ninth Annual Scientific Meeting of the American Society of Cytology, November 2-7, 1981, St. Louis, Missouri. 90 pp., 1981.

Four major nuclear alterations in normal and neoplastic cells are related to nuclear structures in the mitotic cycle: telophase, S phase early and late prophase. In malignant tumor cells, these nuclear structures are associated with lack of differentiation and with the probability of cellular commitment to division. Conversely, tumor associated morphological markers occur in cell nuclei as a result of a mitotic arrest in either the early or late prophase, and remain unchanged throughout cell differentiation. In patients with malignant tumors well differentiated cells adjacent to and distant from the neoplasm have tumor markers consisting of nuclear structures similar to those of malignant tumor cells. The malignant potential of histologic alterations, such as dysplasia, polyps, ulcerative colitis, pernicious anemia and others, may be identified by presence of tumor markers in cells of tissues prior to their malignant transformation. Experimental induction of nuclear tumor markers in vivo by low dose carcinogenesis, and in vitro by leukemic lymphocyte DNA, and presence of lymphocyte tumor markers in normal individuals with a family history of neoplasms, points to a possible role of this nuclear alteration in the biology of cancer. (no Refs)

78. T-CELL GROWTH FACTOR AND THE ESTABLISHMENT OF CELL LINES FROM HUMAN T-CELL NEOPLASIAS (MEETING ABSTRACT).

Ruscetti FW, Gootenberg J, Gallo RC
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

Normal human T-cells activated by either antigen or lectin have been maintained in continuous culture for over 1 yr provided that they were supplemented every 3-5 days with conditioned media from lectin-stimulated mononuclear cells. A protein designated T-cell growth factor (TC-GF) is responsible for this growth promotion. TCGF stimulated only the proliferation of previously activated T-cells and had no effect on resting T-cells. This discovery that T-cells had to be activated before acquiring responsiveness to TCGF suggested that malignant T-cells activated by the transforming process could selectively proliferate in direct response to TCGF. Long-term growth dependent on the addition to TCGF occurred in 22 out of 27 cases of cutaneous T-cell lymphoma and 8 out of 13 cases of T-cell acute lymphocytic leukemia (ALL). Two of these cultured cell lines (HUT102 and CTCL-2) originally dependent on addition of TCGF for in vitro growth sequentially become independent of TCGF for growth. If a subset of T-cells do, in fact, have the capacity to elaborate TCGF and malignant T-cells retain their ability to respond to it, then self-replicating malignant T-cells could have a selective growth advantage. Conditioned media (CM) from HUT102 concentrated 20x by amnonium sulfate precipitation can maintain the growth of normal T-cells. No CM from B-cell lines (10 samples), factor independent ALL cell lines (15 samples) or other cell lines that we tested are able to support growth of human T-cells. (no Refs)

79. DEMONSTRATION OF HETEROGENEITY IN A CELL LINE FROM A HUMAN UROTHELIAL TUMOUR (MEETING ABSTRACT).

Hastings RJ, Franks LM

Imperial Cancer Research Fund, Lincoln's Inn Fields, London WC2A 3PX, England

Cell Biol Int Rep; 5(SupplA):23 1981

Seven populations of cells were clonally isolated from a human urothelial carcinoma-derived cell line (EJ). The parent cell line had a heterogeneous chromosome constitution and showed a transformed phenotype in that it grew in agar and produced tumors in nude mice. Each clone was chromosomally unique; three clones had a pseudo-diploid chromosome constitution and four had either hypo- or hyper-tetraploid chromosome modes. All seven clones formed colonies in agar, but with widely varying (0.5-9%) efficiencies. Six of the clones produced sc tumors in nude mice. The seventh clone, which had a high colony forming efficiency in agar, did not produce tumors in nude mice, confirming other findings that these two commonly used markers of transformation are not always associated in epithelial cells. The phenotypes of the clones were stable until at least passage number 40 in vitro. Specific chromosome aberrations, detectable by G-banding techniques, were associated with colony forming efficiency and tumorigenicity as previously proposed. (3 Refs)

ASSAYS OF ONCOGENIC TRANSFORMATION

80. NEOPLASTIC TRANSFORMATION OF HUMAN EPITHELIAL CELLS IN VITRO AFTER EXPOSURE TO CHEMICAL CARCINOGENS.

Milo GE, Noyes I, Donahoe J, Weisbrode S

Comprehensive Cancer Center, Ohio State Univ., 410 West 12th Ave., Columbus, OH, 43210

Cancer Res; 41(12):5096-5102 1981

Human foreskin epithelial cells were transformed to an anchorage-independent state of growth (in soft agar) and neoplasia (invasion of chick embryonic skin in vitro). Aflatoxin B1, N-methyl-N'-nitro-N-nitrosoguanidine, propanesultone, beta-propiolactone, or UV absorbance at 254 nm were used successfully as carcinogens. These foreskin epithelial cells, like human foreskin fibroblasts, were readily transformed when treated in S phase but, unlike the transformed fibroblasts, expression of cellular neoplasia did not require an extended period of time in culture. The invasive features of the transformed human epithelial cells in chick embryonic skin in vitro simulated squamous cell carcinoma. (Author abstract) (29 Refs)

81. FRIEND VIRUS TRANSFORMED CELLS IN THE ADVANCED STAGES OF ERYTHROLEUKEMIA.

Mager DL
University of Toronto, Toronto, Canada
Diss Abstr Int [B]; 42(3):886-B 1981

Friend erythroleukemia appears to consist of an early 'preleukemic' phase and a later phase in which truly leukemic or tumorigenic cells appear. Although the early stage of the disease, characterized by splenomegaly and erythroblastosis, has been extensively studied, relatively little is known about the late malignant stage of Friend erythroleukemia. The primary aim of this work was to develop procedures for the detection and characterization of the leukemic cells emerging in the advanced stages of erythroleukemia induced by two distinct strains of Friend leukemia virus. An in vitro colony method has been developed which appears to detect a class of malignant Friend virus-transformed cells specific to the advanced stages of erythroleukemia. This method detects cells, capable of forming macroscopic colonies in methylcellulose, which appear in the spleens of mice late after infection with the anemia-inducing (FV-A) or polycythemia-inducing (FV-P) strain of Friend virus. The progeny of these colony-forming cells produce Friend virus, are capable of forming spleen colonies in irradiated syngeneic hosts, are tumorigenic, and can be established as permanent erythroid cell lines. An in vivo spleen colony method has also been developed that detects a class of cells appearing late after infection with Friend virus. These cells are able to proliferate to form macroscopic spleen colonies in irradiated S1/S1d mice. Mice of this genotype have a defective cellular microenvironment that prevents spleen colony formation by normal hemopoietic stem cells. Thus, these observations form the basis of the first in vivo colony assay for Friend virus transformed cells and demonstrate that these cells have become at least partially independent of a normal cellular regulatory factor. (no Refs)

GENERAL REVIEWS AND OTHER RELATED STUDIES

82. CANCER BIOLOGY.

Ruddon RW
Biological Markers Program, NCI-Frederick Cancer Res. Center, Frederick, MD
Cancer Biology. New York, Oxford University Press, 344 pp., 1981.

Cancer biology is reviewed, from basic mechanisms of carcinogenesis to the etiology and pathophysiology of human cancer. Emphasis is placed on the molecular mechanisms involved in malignant transformation of cells and in the pathological changes that occur in an experimental animal or in a patient with cancer. Evidence for the various proposed causes of cancer is presented and discussed. Subjects include the nature of malignant tumors, incidence, epidemiology, and etiology of human cancer, regulation of cellular differentiation, cellular differentiation in cancer, phenotypic characteristics of transformed malignant cells, the cause of the phenotypic derangement of the cancer cell, tumor growth in vivo and host-tumor interactions, and some future prospects for preventing and curing cancer. (813 Refs)

83. ON THE MOLECULAR BASIS OF ONCOGENESIS.

Ahlgren JD
Div. Medical Oncology, Vincent T. Lombardi Cancer Res. Center, Georgetown Univ. Sch. Medicine, Washington, DC, 20007
J Theor Biol; 93(1):215-223 1981

A molecular basis for the development of neoplasia is proposed based on viral disruption of genomic regions coding for proteins which control entry into the cell cycle from Go. Such disruption could also be effected by chemically or radiation-induced mutation. Under such conditions normal control proteins would no longer be synthesized. As the available intracellular pool of normal protein is used up, more and more cells would remain in the proliferative cycle. Fetal genes might also be derepressed, with a concomitant reduction in the expression of adult genes, resulting in a shift in transformed cells toward a less differentiated state. The expression of derepressed fetal genes would account for observed fetal antigens on tumor cells. The somatic cell destined to form a tumor clone may have multiple abnormal intracellular proteins due to the random nature of simultaneous point mutations in the genome. Endogenous transposable elements may also cleave control cistrons. (35 Refs)

84. THE ROLE OF GENE DOSAGE AND GENETIC TRANSPOSITIONS IN CARCINOGENESIS.

Klein G
Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm, Sweden
Nature; 293(5839):313-318 1981

Analysis of chromosome translocations associated with B-cell derived tumors and studies of chromosome-15 trisomy in murine leukemia support the theory, emerging from recent work on tumor viruses, that cancer can be associated with DNA rearrangements which result in the increased expression of normal cellular genes. (Author abstract) (87 Refs)

85. LIVER CARCINOGENESIS: THE ROLE FOR SOME CHEMICALS OF AN EPIGENETIC MECHANISM OF LIVER-TUMOR PROMOTION INVOLVING MODIFICATION OF THE CELL MEMBRANE.

Williams GM
Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Food Cosmet Toxicol; 19(5):577-583 1981

A number of chemicals, including phenobarbitals, DDT, and polychlorinated biphenyl, are hepatocarcinogenic in mice and rats after prolonged exposure; they lack genotoxic action and have been suggested to be epigenetic carcinogens. Because several of these chemicals enhance the effect of genotoxic carcinogens under conditions in which they are not themselves carcinogenic, they are probably of the promoter class of epigenetic carcinogens. Mechanism of promotion may involve (1) completion of conversion of partially transformed cells to full neoplastic cells, or (2) inhibition by the promoter of intercellular communication. The first mechanism has been demonstrated in skin-tumor promoters (phorbol esters and teleocidin B), whereas the latter mechanism has been demonstrated in studies in which tumor promoters inhibited intercellular communication in fibroblast- and liver-cell cultures. Inhibition by DDT of metabolic cooperation between hepatocytes and adult rat-liver epithelial-thioguanine-resistant mutant cells is described. The theory that tumor promoters interfere with transmission of regulatory factors from normal to spontaneously transformed cells is consistent with the dose-response characteristics of epigenetic promoter hepatocarcinogens. (37 Refs)

86. ROLE OF VIRUSES IN THE ETIOLOGY OF NATURALLY OCCURRING FELINE LEUKEMIA.

Essex M, Grant CK, Cotter SM, Hardy Jr WD
Dept. Microbiology, Harvard Sch. Public Health, 665 Huntington Ave., Boston, MA, 02115
Haematol Blood Transfus; 26:483-487 1981

The biology and natural history of the feline retroviruses and the diseases they cause are reviewed. The feline leukemia viruses (FeLV) cause several forms of leukemia and lymphoma that occur at different rates in different geographic areas; no specific association between naturally occurring disease and any strain(s) of any subgroup(s) has been demonstrated. FeLVs are replication competent and cause no visible pathology in infected cultured cells. FeLVs are transmitted in a contagious manner. Approx 2-5% of infected cats become persistently viremic, and one-fourth to one-third of these animals develop leukemia (the other develop infectious peritonitis, septicemia, or glomerulonephritis). Both leukemic and persistently viremic cats release large amounts of infectious FeLV in their saliva. FeLV appears to play an important role in the etiology of 'virus-negative' leukemia in cats; an understanding of the mechanism of this phenomenon may help us to explain human leukemias that occur in individuals that do not harbor replicating virus. FeLV particles contain seven distinct proteins, several of which have greater than 1 antigenic determinant and all of which induce immune responses in cats to some degree. The feline oncornavirus-associated cell membrane antigen (FOCMA) is found on lymphoma and/or leukemia cells, and the immune response to it is correlated with protection against development of leukemia and lymphoma. Two general classes of tumor- and transformation-specific antigens have been found. (39 Refs)

87. OB ODNOM IZ VOZMOZHNYKH MEKHANIZMOV REGULIATSII ROSTA MNOGOKLETOCHNYKH ORGANIZMOV I EGO PRILOZHENII K PROBLEMAM STARENIIA I KANTSEROGENEZA] [ONE OF THE POSSIBLE MECHANISMS OF GROWTH REGULATION OF MULTICELLULAR ORGANISMS AND ITS APPLICABILITY TO THE PROBLEMS OF AGING AND CARCINOGENESIS.

Mustafin AM
Kazakh Inst. Oncology and Radiology, Alma-Ata, USSR
Usp Sovrem Biol; 92(2):261-277 1981

The role of nucleoproteins containing redundant DNA or heterogenous RNA in regulation of the growth of multicellular organisms is reviewed, with special emphasis on the mechanisms of aging and carcinogenesis. It is suggested that malignant transformation is associated with intensive tumor cell death and thus with accumulation of degradation products, including fragments of redundant DNA and RNA. (165 Refs) (In RUS)

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Calabrese EJ
Environmental Health Program, Div. Public Health, Univ. Massachusetts, Amherst, MA
Nutrition and Environmental Health: The Influence of Nutritional Status on Pollutant Toxicity and Carcinogenicity. Volume 2: Minerals and Macronutrients. New York, John Wiley and Sons, 468 pp., 1981.

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

2. RETROSPECT AND PROSPECT OF STUDIES ON DIGESTIVE SYSTEM DISEASES IN CHINA.
Zhang X
Dept. Internal Medicine, Capital Hosp., Chinese Acad. Medical Sciences, Beijing, People's Republic of China
Zhonghua Xiaohua Zazhi; 1(1):1-4 1981
In CHI

3. EPIDEMIOLOGY OF PITUITARY ADENOMAS.
Gold EB
Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 Wolfe St., Baltimore, MD, 21205
Epidemiol Rev; 3:163-183 1981

4. BLADDER CANCER EPIDEMIOLOGY.
Matanoski GM, Elliott EA
Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 North Wolfe St., Baltimore, MD, 21205
Epidemiol Rev; 3:203-229 1981

5. THE EPIDEMIOLOGY OF BENIGN BREAST DISEASE.
Ernster VL
Dept. Epidemiology and International Health, 1699HSW, Univ. California, San Francisco, CA, 94143
Epidemiol Rev; 3:184-202 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

6. AIR POLLUTION AND BIOLOGICAL DEFENCE.
Schlipkoter HW, Dolgner R
Med. Institut fur Umwelthygiene an der Univ., Gurlittstrasse 53, D-4000 Dusseldorf 1, W. Germany
Zentralbl Bakteriol [Orig A]; 172(4/5):299-311 1981
In GER

7. CANCER AND THE PHYSICOCHEMICAL QUALITY OF DRINKING WATER IN QUEBEC.
Thouez JP, Beauchamp Y, Simard A
Dept. Geography, Univ. Montreal, Montreal, Quebec, Canada
Soc Sci Med [Med Geogr]; 15(1):213-223 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

8. ONCOGENIC VIRUSES.
Wyke JA
Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England
J Pathol; 135(1):39-85 1981

9. ROLE OF VIRUSES IN THE ETIOLOGY OF NATURALLY OCCURRING FELINE LEUKEMIA.
Essex M, Grant CK, Cotter SM, Hardy Jr WD
Dept. Microbiology, Harvard Sch. Public Health, 665 Huntington Ave., Boston, MA, 02115
Haematol Blood Transfus; 26:483-487 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

10. MAMMALIAN IN VIVO AND IN VITRO CYTOGENETIC ASAYS: A REPORT OF THE U.S. EPA'S GENE-TOX PROGRAM.
Preston RJ, Au W, Bender MA, Brewen JG, Carrano AV, Heddle JA, McFee AF, Wolff S, Wassom JS
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 87(2):143-188 1981

11. BACTERIAL SYSTEMS FOR CARCINOGENICITY TESTING.
Mohn GR
Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Wassenaarseweg 72, 2333 AL Leiden, The Netherlands
Mutat Res; 87(2):191-210 1981

12. MUTAGENESIS BY CHEMICAL AGENTS IN V79 CHINESE HAMSTER CELLS: A REVIEW AND ANALYSIS OF THE LITERATURE.
Bradley MO, Bhuyan B, Francis MC, Langenbach R, Peterson A, Huberman E
Merck Inst. for Therapeutic Res., West Point, PA, 19486
Mutat Res; 87(2):81-142 1981

OTHER REVIEWS IN CARCINOGENESIS

13. CANCER BIOLOGY.
Ruddon RW
Biological Markers Program, NCI-Frederick Cancer Res. Center, Frederick, MD
Cancer Biology. New York, Oxford University Press, 344 pp., 1981.

14. AVOIDABLE CANCER: ATTRIBUTION OF RISK.
Doll R
Radcliffe Infirmary, Oxford, England
S Afr Cancer Bull; 25(3):125-146 1981

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TRANSFORMATION GENE STRUCTURE

1. SPECIFIC INTEGRATION OF REV PROVIRUSES IN AVIAN BURSAL LYMPHOMAS.

Noori-Daloii MR, Swift RA, Kung HJ, Crittenden LB, Witter RL
(c/o Kung) Dept. Biochemistry, Michigan State Univ., East Lansing, MI, 48824
Nature; 294(5841):574-576 1981

The structure of non-defective reticuloendotheliosis virus (nd Rev) proviruses in bursal lymphomas was characterized. The DNAs extracted from bursal tumors induced by the chick syncytial virus (CSV) strain of nd Rev were digested with restriction endonucleases, electrophoresed in agarose gels, and hybridized to probes specific for the nd Rev genomes and the oncogene of MC-29 virus. Linkage between REV proviruses and the c-myc gene was determined by EcoRI endonuclease digestion and confirmed by digestion with other restriction enzymes. The results suggested that in each tumor, at least one REV provirus was integrated next to the c-myc gene (on 1/2 homologous chromosomes); the latter gene was strongly implicated in lymphomagenesis. The REV proviruses in 22/25 tumors characterized were linked to c-myc. The sizes of the EcoRI linkage fragments varied from 11 to 22 kilobases (kb). The majority of viral sequences appeared to be present in the proviruses. Thus, structural alterations giving rise to the shortened 11-kb tumor-specific (TS) band probably involved the surrounding cellular sequence. The high intensity of the 11-kb TS band, along with its larger size compared to the unintegrated viral DNA, suggested that amplification of REV provirus and of its surrounding cellular sequences had occurred. Tumors 1 and 8 contained eight and one copies of the proviral sequences, respectively. Structural alteration in the REV provirus and its adjacent cellular sequences are discussed in relation to transformation. (23 Refs)

2. NUCLEOTIDE SEQUENCE OF THE GENOME OF A MURINE SARCOMA VIRUS.

Van Beveren C, Van Straaten F, Galleshaw JA, Verman IM
Tumor Virology Lab., Salk Inst., San Diego, CA, 92138
Cell; 27(1,part2):97-108 1981

The complete nucleotide sequence of a molecularly cloned, biologically infectious mouse sarcoma virus DNA has been determined. It is 5,833 nucleotides in length. It contains two long terminal repeats, the coding capacity for the entire gag gene, portions of the pol gene and the entire transforming gene. Synthesis of the 538 amino acid-long gag gene-encoded polyprotein Pr62gag initiates 596 nucleotides downstream from the 5'-cap nucleotide. The cleavage of gag polyprotein to mature core proteins, NH2-p15-p12-p30-p10-COOH, does not involve the loss of any amino acids. The complete nucleotide sequence of the cellular homolog (c-mosMo) of viral transforming gene v-mosMo has been determined. There are 25 single-base changes in an uninterrupted sequence of 1,157 nucleotides. Of these, 21 changes are in the coding region and they alter only 11 amino acids with respect to v-mosMo gene product. The homologous and nonhomologous regions between mouse sarcoma viral DNA and its progenitor, murine leukemia virus DNA, have been identified. Most deletions appear to have occurred by homologous recombination. A sequence GACC or its inverse GGTC is present in the vicinity of all substitutions and deletions. The codon usage of the gag gene is quite different from that of the c-mosMo gene. (Author abstract) (73 Refs)

3. NUCLEOTIDE SEQUENCE OF THE TRANSFORMING EARLY REGION E1B OF ADENOVIRUS TYPE 12 D NA: STRUCTURE AND GENE ORGANIZATION, AND COMPARISON WITH THOSE OF ADENOVIRUS TYPE 5 DNA.

Kimura T, Sawada Y, Shinnawawa M, Shimizu Y, Shiroki K, Shimojo H, Sugisaki H, Takanami M, Uemizu Y, Fujinaga K
Cancer Res. Inst., Sapporo Medical Coll., Sapporo 060, Japan
Nucleic Acids Res; 9(23):6571-6589 1981

The nucleotide sequence of the entire transforming early region Elb of the highly oncogenic adenovirus Type 12 (Ad12) DNA has been determined. The total sequence (3860 base pairs) encompasses the entire transforming early region E1 of AD12 DNA. From the sequence for the Elb region of Ad12, and the transcription map of the Elb region the structure and gene organization of the early region Elb of Ad12 DNA were analyzed and compared with those of the Elb region in the non-oncogenic Ad5 DNA. Most of the sequences in the Elb region of Ad12 was highly homologous to that of Ad5. It is predicted that the Ad12 region Elb codes for polypeptides of 53.9, 19.1, and 8.9 kd. This situation is identical with that of the Ad5 region Elb which codes for polypeptides of 54.9, 20.6, and 8.3 kd. The function of these predicted polypeptides encoded by the Elb regions in cell transformation is discussed. (Author abstract) (41 Refs)

4. TRANSFORMATION BY ADENOVIRUS EARLY REGION 2A TEMPERATURE-SENSITIVE MUTANTS AND THEIR REVERTANTS.

Logan J, Nicolas JC, Topp WC, Girard M, Shenk T, Levine AJ
Dept. Microbiology, State Univ. New York, Sch. Medicine, Stony Brook, NY, 11794
Virology; 115(2):419-422 1981

H5ts107 is a temperature-sensitive (ts) mutant of adenovirus Type 5 whose alteration maps in the structural gene for the viral DNA binding protein. Temperature-independent revertants of this mutant that form plaques at 39 C in HeLa cells have been isolated. These revertants fall into two classes: (1) ts+ revertants for growth and plaque formation at 39 C in both HeLa cells and 293 cells, a human cell line transformed by Type 5 adenovirus; (2) ts+ for growth and plaque formation at 39 C in HeLa cells, but ts for growth and plaque formation in 293 cells. The frequency of rat cell transformation by H5ts107 was fivefold higher than that of wild-type adenovirus. A Class 1 revertant, r(st107)127, transformed cells at the wild-type virus frequency while a Class 2 revertant, r(ts107)202, retained the ability to transform cells at the higher frequency. When the XhoI-C DNA fragment from these viruses, which contains the left end 15.5% of the viral genome, was employed to transform rat cells, then Ad5 wt, H5ts107, r(ts107)127, and r(ts107)202 DNAs all transformed with approximately equal frequencies. (Author abstract) (17 Refs)

5. INTEGRATION OF FOREIGN GENOME FRAGMENTS INTO CELLS TRANSFORMED OR COTRANSFORMED WITH FRAGMENTED ADENOVIRAL DNA.

Tikchonenko TI, Chaplygina NM, Kalinina TI, Gartel AL, Ponomareva TI, Naroditsky BS, Dreizin RS
D. I. Ivanovsky Inst. Virology, Acad. Medical Sciences USSR, Moscow 123098, USSR
Gene; 15(4):349-359 1981

DNA integration of highly oncogenic simian adenovirus type 7 (SA7) and non-oncogenic human adenovirus type 6 (Ad6) into the genome of newborn rat kidney cells transformed by fragmented DNA preparations was studied. SA7 and Ad6 transformation, expression of integrated viral sequences, Ad6-pBR322 plasmid cointegration comprised the study. Intact DNA transformation, transformation by fragmented DNA, shortening of integrated DNA, and competence of eukaryotic cells are discussed. Reassociation kinetics and spot hybridization were employed. DNA was fragmented with the specific endonucleases SalI and endonuclease BglII. Cells transformation by fragmented DNA resulted in integration of the left-hand fragment and other regions of the viral genome with the oncogene. Integrated fragments were stable during numerous passages of cell lines. In the case of the Ad6-transformed cell line integrated fragments were not expressed. Mass losses of 25-50% occurred with the integration of SA7 DNA fragments. The linear form of pBR322 plasmid contributed to the Ad6 DNA integration into the genome of the transformed cell. (40 Refs)

TRANSFORMATION GENE EXPRESSION AND REGULATION

6. ROUS SARCOMA VIRUS TRANSFORMING PROTEIN, P60SRC, EXPRESSED IN E. COLI, FUNCTIONS AS A PROTEIN KINASE.

Gilmer TM, Erikson RL
Dept. Pathology, Univ. Colorado Health Sciences Center, Denver, CO, 80262
Nature; 294(5843):771-773 1981

Rous sarcoma virus (RSV) p60src produced by Escherichia coli which carry plasmids expressing the src gene was selected by immunoaffinity chromatography and tested for expression of protein kinase (PK) activity. The p60src virus phosphorylated tyrosine residues in tubulin and casein substrates; phosphorylation was inhibited by anti-p60src IgG in a reaction that resulted in phosphorylation of the immune IgG. No PK activity was detectable in bacterial preparations lacking the src gene. Expression of p60src-specific PK activity in E coli suggests that the enzyme activity observed in eukaryotic cells is encoded in the src gene. (25 Refs)

7. ANALYSIS OF TRANSFORMING GENE PRODUCTS FROM MOLONEY MURINE SARCOMA VIRUS.

Papkoff J, Lai MH, Hunter T, Verma IM
Dept. Biology, Univ. California, San Diego, La Jolla, CA, 92093
Cell; 27(1,part2):109-119 1981

We previously showed that in vitro translation of M-MuSV virion RNA yielded a 62 kd gag gene product and an overlapping set of four proteins with approx mol wt of 37,000, 33,000, 24,000 and 18,000. In this paper we show, by use of hybrid arrest translation with cloned recombinant DNAs containing M-MuSV v-mosMo sequences, that the 37, 33, 34 and 18 kd proteins are synthesized in their entirety from the v-mosMo gene. Analysis of the primary sequence of these proteins shows that each one is initiated independently from AUG codons within the v-mosMo gene and utilizes the long open reading frame predicted from the v-mosMo DNA sequence. Antisera against synthetic peptides corresponding to the C terminus of the predicted v-mosMo gene product precipitate all four in vitro v-mosMo proteins. (Author abstract) (39 Refs)

8. IDENTIFICATION OF A 20,000-DALTON PROTEIN IN SSV-TRANSFORMED NONPRODUCER CELLS.

Thiel HJ, Matthews TJ, Weinhold KJ, Broughton EM
Bundesforschungsanstalt fur Viruskrankheiten der Tiere, P.O. Box 1149 Paul Ehrlich-Strasse 28, Tubingen, W. Germany
Virology; 115(2):401-405 1981

Simian sarcoma virus-transformed nonproducer cells (SSV-NP cells) express a 20,000-dalton protein (p20), which is precipitated by an autologous antiserum against SSV-NP cells. The molecule is shed or secreted from the cells because it was found in cell extracts as well as tissue culture supernatants. P20 was detected in SSV-transformed cells from three different species, but not in helper virus (SSAV)-infected nontransformed cells. The data suggest that the expression of p20 is specific for transformation by SSV. (Author abstract) (14 Refs)

9. REVERTANTS OF RAT CELLS TRANSFORMED BY AVIAN ERYTHROBLASTOSIS VIRUS.

Quade K, Saule S, Stehelin D, Kitchener G, Hayman MJ
Div. Virology, Natl. Inst. Medical Res., Mill Hill, London NW7 1AA, England
Virology; 115(2):322-333 1981

Morphological revertants of the avian erythroblastosis virus (AEV)-transformed rat cell line AT1a were isolated and characterized. The revertants are similar to the uninfected parental rat cell line in that they have regained an organized cytoskeleton and they are no longer capable of anchorage-independent growth. The pattern of integrated viral DNA in the revertants is indistinguishable from that of the transformed parent. However, the revertants do not express the integrated viral genome at either the mRNA or protein level. Phenotypic reversion thus is probably due to reduced transcription of the AEV-transforming gene below a threshold necessary to induce morphological transformation. (Author abstract) (45 Refs)

10. VIRAL MESSENGER RNAS IN SIX LINES OF ADENOVIRUS-TRANSFORMED CELLS.

Lewis JB, Mathews MB
(c/o Mathews), Cold Spring Harbor Lab., P.O. Box 100, Cold Spring Harbor, NY, 11724
Virology; 115(2):345-360 1981

We have compared the proteins translated in vitro using virus-specific mRNA from six lines of adenovirus-transformed cells (F4, F17, F19, REM, T2C4, and 293) with those made using RNA from productively infected cells. The mRNAs for proteins E1A-58K, 54K, 48K, and 42K, and for E1B-15K, were detected in all cell lines and for E1B-57K in at least five of the lines. Neither of the minor E1A mRNAs (for proteins 25K and 28K) found under specific conditions in infected cells were found in any transformed cell line. Two cell lines, F4 and T2C4, contained small amounts of other mRNAs encoded within region E1B including in the latter case one not detected in infected cells. The lines F4, REM, and T2C4 contain at least some E4 mRNAs, again including in the latter case one not detected in infected cells. T2C4 cells also contain E3 mRNAs, E2A-72K protein mRNA, and two E2B mRNAs, although the 32B proteins are not identical to any found in infected cells. The F19 and T2C4 lines express mRNAs encoded between 11 and 17 map units, the 'IVa2 region', but do not include the mRNA for polypeptide IVa2 itself. Some early mRNAs, including the 'immediate early' mRNAs, have not been detected in any of these lines of transformed cells: nor did the cell lines contain any mRNAs found exclusively at late times during productive infection. Comparison of these results with the properties of the cells tentatively suggest a correlation (although not necessarily causal) between the expression of additional viral genes and increased tumorigenicity. (Author abstract) (58 Refs)

GENETIC AND OTHER HOST FACTORS WHICH MODULATE ONCOGENIC TRANSFORMATION

11. INDUCTION OF LYMPHOMAS AND TUMOR ANTIGEN BY MAREK'S DISEASE VIRUS IN TURKEYS.

Elmubarak AK, Sharma JM, Witter RL, Nazerian K, Sanger VL
U. S. Dept. Agriculture, SEA-AR, Regional Poultry Res. Lab., 3606 E. Mount Hope Road, East Lansing, MI, 48823
Avian Dis; 25(4):911-926 1981

Mycoplasma-free turkeys were inoculated with the highly pathogenic GA isolate of Marek's disease (MD) virus (MDV), and were observed for lympholytic and lymphoproliferative lesions and humoral and cellular immunocompetence. Inoculated turkey poults became persistently viremic with MDV, with levels of circulating MDV that were lower than in similarly inoculated specific-pathogen-free chickens. The early lytic phase of MD with lymphoid cell destruction and appearance of viral antigen in lymphoid organs was less pronounced than in chickens. Gross lesions in turkey poults after MDV infection were most frequent in spleen and liver but also involved kidneys, gonad, heart, thymus, and peripheral nerves. MD tumors contained cells that reacted with antiserum prepared against chicken MD-tumor-associated surface antigen. This result indicated that MDV induced cellular transformation in turkeys and that the tumor-associated antigen in chickens and turkeys cross-reacted. Several in vitro-propagating B-cell lines were developed from turkey lymphomas. MD in turkeys resulted in immunodepression as it did in chickens. Circulating lymphocytes from turkeys that eventually died of MD or had developed gross tumors were deficient in response to Concanavalin A. (19 Refs)

EXPERIMENTAL MODULATION OF ONCOGENIC TRANSFORMATION

12. EXPRESSION OF INITIATED AND PROMOTED STAGES OF IRRADIATION CARCINOGENESIS IN VITRO.

DiPaolo JA, DeMarinis AJ, Evans CH, Doniger J
Lab. Biology, NCI, Bethesda, MD, 20205
Cancer Lett; 14(3):243-249 1981

The temporal dynamics of 12-O-tetradecanoylphorbol-13-acetate (TPA)-promoted transformation in vitro and the sensitivity of initiation and promotion to lymphotoxin were investigated. Syrian hamster embryo cells (HEC) initiated by x-irradiation (300 R) were treated with TPA 48 hr later for transformation induction. TPA treatment resulted in a 15-20x enhancement of x-ray induced transformation. When cells were irradiated on day 1 and treated with TPA on days 3, 4, or 5 of the 7-day experiment, similar transformation frequencies resulted, indicating that TPA is required only for the last 2 days. All cells appeared to be initiated on day 3. However, the presence of TPA from days 3-5 was found to be insufficient for max transformation. Since a return to levels of transformation obtained by x-irradiation alone occurs with decreasing intervals of TPA exposure, the promotion phenomenon is apparently reversible. Both TPA-dependent and TPA-independent initiation occurs after x-irradiation in this system. Lymphotoxin was found to inhibit TPA enhancement of UV or x-irradiation transformation of HEC. (15 Refs)

13. HYPERTHERMIC MODULATION OF X-RAY-INDUCED ONCOGENIC TRANSFORMATION IN C3H 10T1/2 CELLS.

Clark EP, Hahn GM, Little JB

Dept. Radiation Medicine, Massachusetts General Hosp., Boston, MA, 02114

Radiat Res; 88(3):619-622 1981

The effect of hyperthermia on the malignant transforming potential of x-rays was studied in the C3H mouse embryo cell line (10T1/2, clone 8). No transformed foci developed in non-treated cultures or in cultures exposed to hyperthermia alone. When hyperthermia was combined with x-rays, either a 43 C/ 60 min or a 45 C/15 min hyperthermic exposure preceding a 200-rad x-ray exposure, produced a 4-5-fold enhancement in mean transformation frequency as compared with that induced by x-rays alone. The yield of transformants for cells exposed to 200 rad following incubation at 43 C for 60 min was significantly higher than for those exposed to 200 rad alone (0.02 less than P less than 0.05). Heating times were important since shorter hyperthermic exposures did not result in transformation frequencies significantly higher than that induced by x-rays alone. A similar trend was also observed when transformation was scored on a per dish basis. The results suggested that the possibility of treatment-induced neoplasms should be considered before the design of combined hyperthermia-radiation treatment plans. (10 Refs)

14. SIMILARITIES AND DIFFERENCES BETWEEN THE EFFECTS OF EPIDERMAL GROWTH FACTOR AND ROUS SARCOMA VIRUS.

Cooper JA, Hunter T

Tumor Virology Lab., Salk Inst., San Diego, CA, 92138

J Cell Biol; 91(3):878-883 1981

We have derived a line of A431 human tumor cells infected with Rous sarcoma virus (RSV). The infected cells contain the RSV-transforming protein, pp60src, which has characteristic tyrosine-specific protein kinase activity. As in other RSV-transformed cells, a 36,000-dalton protein is phosphorylated in RSV-infected A431 cells. Addition of epidermal growth factor (EGF) to the cells induces further phosphorylation of this protein. In contrast, this phosphoprotein is not detected in uninfected A431 cells, except when treated with EGF. Increased phosphorylation of the EGF receptor protein and of an 81,000-dalton cellular protein is dependent upon addition of EGF to the culture fluids, in both control and RSV-infected A431 cells. The results are discussed with reference to the similarities and differences between the tyrosine-specific protein kinases induced by RSV and activated by EGF. (Author abstract) (42 Refs)

15. INTERTISSUE VARIATION IN BENZO(A)PYRENE METABOLISM BY HUMAN SKIN, LUNG AND LIVER IN VITRO.

Milo GE, Trewyn RW, Tejwani R, Oldham JW, Douglas WH
Dept. Physiological Chemistry, Ohio State Univ., Columbus, OH
Aerosp Med Biol; (224):173 1981

An environmental agent benzo(a)pyrene (B(a)P), is shown to transform human skin fibroblasts in vitro. This fossil fuel combustion product and other polynuclear hydrocarbons have exhibited a requirement to be biotransformed to their ultimate carcinogenic forms to induce transformation. B(a)P diol-epoxides are the most cited candidates as ultimate carcinogens. Results suggest that either the ultimate form of the carcinogen is different for fibroblasts and epithelial cells or the quantitative generation of hydroxylated metabolites is not required for neoplastic transformation in fibroblast cells. If hydroxylation is required, then the site of hydroxylation may be the significant factor. Present evidence suggests that in B(a)P treated fibroblasts the activation of B(a)P in the cell takes place other than the microsomal P450 complex, presumably in the nucleus. (Author abstract) (no Refs)

BIOCHEMICAL AND MOLECULAR BIOLOGICAL STUDIES OF TRANSFORMED PHENOTYPE

16. IDENTIFICATION OF A NUCLEAR AND OF A CYTOPLASMIC POLYPEPTIDE WHOSE RELATIVE PROPORTIONS ARE SENSITIVE TO CHANGES IN THE RATE OF CELL PROLIFERATION.

Bravo R, Fey SJ, Bellatin J, Larsen PM, Arevalo J, Celis JE
(c/o Celis) Div. Biostructural Chemistry, Dept. Chemistry, Aarhus Univ., DK-8000 Aarhus, Denmark
Exp Cell Res; 136(2):311-319 1981

A 36K MW polypeptide was previously identified by two-dimensional gel electrophoresis whose relative proportion increases in S phase of HeLa cells, and following viral transformation of mouse 3T3B and hamster BHK21 cells. We report here experiments that show that this polypeptide (isoelec tric focusing (IEF 49)) is localized in the nucleus and that its relative proportion decreases dramatically under conditions for which there is a decrease in the rate of cell proliferation, due for example, to the formation of giant HeLa cells by X-ray irradiation or the senescence of human skin fibroblasts. It is present in negligible amounts in non-cycling cells of adult tissues. These studies also revealed an unrelated cytoplasmic polypeptide (IEF 52; tropomyosin related; coordinates 35/1.43) whose relative proportion increased significantly and reproducibly with a decrease in the rate of cell proliferation. It is suggested that IEF 49 may be a useful marker for cycling cells. (Author abstract) (28 Refs)

17. ALTERATIONS IN ELECTROPHYSIOLOGY OF CULTURED BALB/CFC3H MOUSE MAMMARY EPITHELIUM ASSOCIATED WITH NEOPLASTIC TRANSFORMATION.

Bisbee CA
NIH, Room 6N-307, Building 10, Bethesda, MD, 20205
Cancer Lett; 14(3):237-242 1981

Prolactin-controlled transepithelial electrophysiological properties associated with the neoplastic state and with the presence of mammary tumor virus in BALB/cfC3H mouse mammary epithelium are described. Short-circuit current values from tumor-cell cultures were observed to be max 20% of prelactating cell culture values. Neoplastic epithelium potential differences were only slightly lower than in prelactating epithelium. Resistances of tumor-cell cultures were not different from those of prelactating cell cultures. The findings suggest a reduction in prolactin sensitivity with expression of mammary tumor virus. Such decreased prolactin sensitivity may result from differential effects of prolactin on the component elements of short-circuit current and resistance. (31 Refs)

MORPHOLOGICAL AND OTHER BIOLOGICAL ASPECTS OF ONCOGENIC TRANSFORMATION

18. DEVELOPMENTAL ONSET OF MIXED-FUNCTION OXIDASE ACTIVITY IN PREIMPLANTATION MOUSE EMBRYOS.

Filler R, Lew KJ

Biology Div., Oak Ridge Natl. Lab., Post Office Box Y, Oak Ridge, TN, 37830

Proc Natl Acad Sci USA; 78(11,part2):6991-6995 1981

Two-cell embryos, obtained from the C57BL/6N and DBA/2N strains, were cultured in media that supported in vitro differentiation and that contained [3H]benzo[a]pyrene. High-pressure liquid chromatography of the activated intermediates formed during in vitro early embryonic development indicated that the onset of polynuclear aromatic hydrocarbon activation coincided with blastocyst formation. Comparison of individual oxygenated intermediates metabolically formed from embryos genetically 'responsive' or 'nonresponsive' to aromatic hydrocarbons revealed significant quantitative differences in the production of dihydrodiol, quinone, and phenolic derivatives. In addition to exhibiting basal mixed-function oxidase activity, blastocysts were also responsive to enzymatic induction when exposed to 2,3,7,8- tetrachlorodibenzo-p-dioxin. The presence of operative metabolite-detoxifying pathways was also assayed. Enzymatic treatment of water-soluble metabolites with beta-glucuronidase or arylsulfatase revealed that neither glucuronic acid conjugates nor sulfate ester derivatives were present. These data, therefore, provide direct evidence that late preimplantation mouse embryos (day 3 1/2 of gestation) are similar to later developmental stages in having the enzymatic capability for xenobiotic activation and enzyme induction but are dissimilar with respect to their detoxification mechanism(s). Moreover, the ability of preimplantation embryos to activate directly polynuclear aromatic hydrocarbon to bioreactive intermediates may be of importance in assessing the ontological susceptibility of the developing embryo to carcinogenic or teratogenic chemicals. (Author abstract) (27 Refs)

19. HEMATOPOIETIC CELLS TRANSFORMED IN VITRO BY REVT AVIAN RETICULOENDOTHELIOSIS VIRUS EXPRESS CHARACTERISTICS OF VERY IMMATURE LYMPHOID CELLS.

Beug H, Muller H, Grieser S, Doederlein G, Graf T
Institut fur Virusforschung, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany
Virology; 115(2):295-309 1981

REVT (avian reticuloendotheliosis virus) is a replication defective acute leukemia virus possessing a transformation-specific sequence designated rel. Hematopoietic cells transformed by REVT in vitro expressed cell surface markers of immature B lymphocytes. Some clones of transformed cells also expressed cell surface determinants of immature T lymphocytes. An antiserum specific for REVT-transformed cells reacted with the cell surface of lymphoid leukemia cells of both the B- and T-cell lineage as well as with a subpopulation of cells in normal spleen, thymus, and bone marrow. REVT-transformed cells did not express surface or cytoplasmic immunoglobulin chains nor terminal deoxynucleotidyl transferase, nor were they susceptible to infectious bursal disease virus. As expected they were also negative for the expression of all erythroid and myeloid differentiation parameters tested. (Author abstract) (53 Refs)

20. HIGHLY-PERMEABLE INTERCELLULAR COMMUNICATIONS AND ELECTRICAL CHARACTERISTICS OF NORMAL LIVER AND HEPATOMA. I. HIGHLY-PERMEABLE INTERCELLULAR COMMUNICATIONS IN INDUCED MURINE HEPATOMA.

Sharovskaia IuIu, Mittel'man LA, Smolianinov VV, Chailakhian LM
Res. Lab. Molecular Biology and Bio-organic Chemistry, M. V. Lomonosov State Univ., Moscow, USSR
Tsitologiia; 23(10):1142-1148 1981

Permeability of the intercellular communications was studied in C3HA mice with o-aminoazotoluene-induced hepatomas. Transmembrane potentials, the input resistance, and distribution of the electric potential measured in hepatoma tissue at different stages of carcinogenesis did not differ from those in normal liver tissue. It was suggested that highly-permeable intercellular communications play a nonspecific role in malignant transformation. (12 Refs) (In RUS)

ASSAYS OF ONCOGENIC TRANSFORMATION

21. INHIBITION OF VIRUS TRANSFORMATION BY HIGH ENERGY FUELS AS A CORRELATE OF CARCINOGENIC POTENTIAL.

Blakeslee JR
Dept. Veterinary Pathobiology, Ohio State Univ., Columbus, OH
Aerosp Med Biol; (224):173 1981

Hydrazine and napthylamines and their derivatives were assayed for co-carcinogenic effects on ST FeSV-directed transformation of human cells. All chemicals tested at non-toxic concentrations showed anti-carcinogenic activity. The temporal relationship of chemical treatment to virus infection was more critical with the hydrazines than with the naphthylamines in that maximum anti-carcinogenic effect occurred when virus-infected cells were exposed to the hydrazine 2 hr post-infection, whereas the naphthylamine anti-carcinogenic effect was observed if cells were exposed either pre- or post-infection. The anti-carcinogenic effect, when compared with in vitro chemical transformation and neoplastic transformation, show a high degree of correlation. These data suggest this assay system may lend itself to a rapid screen (9-13 days) of chemicals for carcinogenic potential. Cytotoxic results showed no significant difference in shale oil or petroleum derived JP5 or DFM. (Author abstract) (no Refs)

GENERAL REVIEWS AND OTHER RELATED STUDIES

22. THE DISSECTION AND RECONSTRUCTION OF GENES AND CHROMOSOMES (NOBEL ADDRESS).

Berg P
Dept. Biochemistry, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
Angew Chem; 93(10):885-893 1981

The development of understanding of the structure and function of genes and chromosomes is reviewed. Early research established that genes controlled the production of proteins. Analysis of DNA from viruses and bacteria disclosed the double-helix structure and purine-pyrimidine base-pair composition of DNA. Studies with polyoma and SV40 viruses allowed mapping of genes producing specific proteins. SV40 was shown to have different life cycles in primate and non-primate cells. Transformation of host cells by SV40 viruses was demonstrated, indicating that viruses could produce heritable changes in host-cell genetic material. Recombination experiments combined viral DNA from SV40 and bacterial DNA from Escherichia coli. Viral and bacterial DNA have since been incorporated into the genome of mammalian cells. Mammalian cells with bacterial genes have been shown to produce bacterial enzymes and to utilize metabolic pathways not used by normal cells. Findings of recombinant genetic studies have potential applications in medicine for correction of genetic defects and other problems. (49 Refs) (In GER)

23. ROLE OF ONCOGENES IN THE DEVELOPMENT OF TUMORS.

Klein G
Institutionen for tumorbiologi, Karolinska institutet, Stockholm, Sweden
Lakartidningen; 78(41):3575-3577 1981

Recent studies in viral oncogenes are reviewed. The coupling of some normal genes is a common feature of all tumor transformation processes caused by not directly-transforming RNA tumor viruses. Unlike the RNA viruses, the DNA viruses belong to several greatly different groups. Production of the so-called T antigen is a common feature of all DNA tumor viruses. This antigen occurs in all transformed cells. There are at least three virus types (papilloma virus, Epstein-Barr virus (EBV), and hepatitis B virus) contribute to the development of certain human tumors, but their contributions are less direct than in the case of infectious diseases. Only papilloma virus induces tumors directly, and most of them are benign, but papilloma virus may play a certain role in the genesis of some malignant epithelial tumors as well. Hepatitis B virus first causes liver cirrhosis, a precancerous state, the development of the tumor clone being the result of abnormal regeneration. (7 Refs) (In SWE)

24. RECENT DISCOVERIES ON CELLULAR PROTEINS IN RELATION TO VIRALLY AND CHEMICALLY INDUCED CARCINOGENESIS.

Jornvall H
Kemiska Institutionen I, Karolinska Institutet, S-104 01 Stockholm, Sweden
Lakartidningen; 78(41):3585-3586 1981

Recent studies on the molecular mechanisms of carcinogenesis suggest the existence of a cellular protein ('53K') common to virally and chemically induced cell transformations. This type of protein binds some T-antigens from oncogenic DNA viruses, including large T-antigen from SV40 and Epstein-Barr virus-determined nuclear antigen. Transformation-related proteins from oncogenic RNA viruses are similar to normal cellular proteins. Several of these proteins have phosphorylating activity, and some of them have been found to be protein kinases. Associations of such proteins with the plasma membrane have also been shown. These different connections between various tumor-related proteins and normal cellular proteins suggest the importance of gene determination in transformations. (11 Refs) (In SWE)

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Witter RL 11

NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

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CHEMICAL CARCINOGENESIS

1. CHEMICAL CARCINOGENESIS.
Farber E
Dept. Pathology, Univ. Toronto, 100 College St., Toronto, ON M5G 1L5, Canada
N Engl J Med; 305(23):1379-1389 1981

2. N-HEXANE AND ITS TOXICOLOGIC EFFECTS. A REVIEW.
Jorgensen NK, Cohr KH
Harevaenget 44, DK-4200 Slagelse, Denmark
Scand J Work Environ Health; 7(3):157-168 1981

3. SAFROLE: ITS METABOLISM CARCINOGENICITY AND INTERACTIONS WITH CYTOCHROME P-450.
Ioannides C, Delaforge M, Parke DV
Dept. Biochemistry, Univ. Surrey, Guildford, Surrey GU2 5XH, England
Food Cosmet Toxicol; 19(5):657-666 1981 -

RADIATION CARCINOGENESIS

4. CARCINOGENIC, MUTAGENIC, TERATOGENIC WORKSHOP.
Suit H, Hall E, Frei E
Dept. Radiation Medicine, Massachusetts General Hosp., Boston, MA, 02114
Cancer Clin Trials; 4(Suppl):37-41 1981

5. DOSIMETRY OF THE ATOMIC BOMB SURVIVORS.
Sinclair WK, Failla P, Bond VP, Loewe WE, Kerr GD, Auxier J, Wyckoff OH, Maruyama T, Schull JW, Land EC, Dobson LR, Mays WC, Seymour J
Argonne Natl. Lab., 9700 South Cass Ave., Argonne, IL, 60439
Radiat Res; 88(3):437-447 1981

DIETARY FACTORS IN CARCINOGENESIS

6. NUTRITION AND CANCER: A REVIEW.
Muller E, Rickenbach M
Institut fur Sozial- und Praventivmedizin, Universitat Zurich, Gloriastrasse 32 B, 8006 Zurich, Switzerland
Praxis; 70(43):1903-1912 1981
In GER

7. FLAVONOIDS, MUTAGENS, AND CITRUS.
Horowitz RM
U. S. Dept. Agriculture, Agricultural Res. Service, Fruit and Vegetable Chemistry Lab., Pasadena, CA, 91106
ACS Symp Ser; 170:43-59 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

8. ETIOLOGICAL CONCEPTS IN CERVICAL CARCINOGENESIS.
Kessler II
Dept. Epidemiology and Preventive Medicine, Univ. Maryland Sch. Medicine, 655 West Baltimore St., Baltimore, MD, 21201
Gynecol Oncol; 12(2,part2):S7-S24 1981

9. CURRENT CONCEPTS ON THE AETIO-PATHOGENESIS OF ACUTE LEUKAEMIA.
Torres A, Martinez Guibelalde F, Gomez Garcia P, Garcia Castellano JM, Manzanares Escribano MR
Jefe Servicio Hematologia, Ciudad Sanitaria 'Reina Sofia' de la Seguridad Social, Cordoba, Spain
Sangre (Barc); 26(5B):700-717 1981
In SPA

10. CANCER FAMILY SYNDROME.
Svendsen LB, Bulow S
Kirurgisk-gastroenterologisk afdeling, Bispebjerg hospital, Copenhagen, Denmark
Ugeskr Laeger; 143(42):2713-2716 1981
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11. GENETIC AND BIOCHEMICAL STUDIES WITH ATAXIA TELANGIECTASIA.
Huang PC, Sheridan RB
Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., Baltimore, MD, 21205
Hum Genet; 59(1):1-9 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

12. THE HEALTH EFFECTS AND ECOLOGICAL SIGNIFICANCE OF CHLORINE RESIDUALS IN WATER.
Kalmaz EV, Kalmaz GD
Univ. Tennessee, Univ. Station 8163, Knoxville, TN, 37916
Chemosphere; 10(10):1163-1175 1981

13. CHEMICAL AND ENVIRONMENTAL AGENTS IN GASTROINTESTINAL CARCINOGENESIS.
Deschner EE, De Cosse JJ, Sherlock P
Lab. Digestive Tract Carcinogenesis, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Clin Gastroenterol; 10(3):755-771 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

14. THE REPAIR OF DNA DAMAGE: RECENT DEVELOPMENTS AND NEW INSIGHTS.
Friedberg EC, Bonura T, Love JD, McMillan S, Radany EH, Schultz RA
Dept. Pathology, Lab. Experimental Oncology, Stanford Univ., Stanford, CA, 94305
J Supramol Struct Cell Biochem; 16(1):91-103 1981

MODIFICATION OF CARCINOGENESIS

15. ROLE OF HORMONES INCLUDING DIETHYLSTILBESTROL (DES) IN THE PATHOGENESIS OF CERVI CAL AND VAGINAL INTRAEPITHELIAL NEOPLASIA.
Robboy SJ, Truslow GY, Anton J, Richart RM
Dept. Pathology, Massachusetts General Hosp., Boston, MA, 02114
Gynecol Oncol; 12(2,part2):S98-S110 1981

16. PROSTAGLANDINS AND CANCER: A REVIEW OF TUMOR INITIATION THROUGH TUMOR METASTASIS.
Honn KV, Bockman RS, Marnett LJ
Dept. Biological Sciences, Wayne State Univ., Detroit, MI, 48202
Prostaglandins; 21(5):833-864 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

17. GENITAL CANCER AND VIRUSES.
Rapp F, Jenkins FJ
Dept. Microbiology, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033
Gynecol Oncol; 12(2,part2):S25-S41 1981

18. VIRUS PAPILLOMAS IN HUMANS.
Nasemann T
Univ.-Hautklinik Eppendorf, Martinistr. 52, D-2000 Hamburg 20, W. Germany
Hautarzt; 32(11):601-606 1981
In GER

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TRANSFORMATION GENE STRUCTURE

1. ALTERED METHYLATION OF ENDOGENOUS VIRAL PROMOTER SEQUENCES DURING MAMMARY CARCINOGENESIS.

Breznik T, Cohen JC
Dept. Microbiology and Immunology, Tulane Univ., Sch. Medicine, New Orleans, LA, 70112

Nature; 295(5846):255-257 1982

The methylation pattern of mouse mammary tumor virus (MMTV) was examined. Origin of the 2.1-and 1.4-kilobase (kb)

HE 20. 3173/2:

HpaII fragments was determined by comparing MspI digests from various inbred mouse strains. Comparison of MspI digestion of DNA from the CBA/CaJ mouse strain (which includes units II and III) with that obtained with DNA from BALB/c (which includes units I, II, and III), indicated that the 2.1-and 1.4-kb MspI-HpaII fragments are derived from the subgenomic unit I. HpaII digestion of DNA from BALB/c mammary tumor 1247 produced several virus-specific fragments in addition to those derived from unit I, indicating that demethylation of other endogenous proviruses has occurred in this tumor. The origin of additional sites of demethylation in tumor 1247 was identified by EcoRI-HpaII double digestions. Demethylation of proviral units during tumorigenesis could be ascertained by determining which EcoRI bands are sensitive to further cleavage by HpaII. Results showed that the methylation pattern of endogenous virus sequences is specifically altered during tumorigenesis in uninfected mice. In addition to transformation by promoter insertion which may occur during exogenous MMTV infection, carcinogenesis by promoter derepression may occur; such an event is suggested by the observed demethylation of either the defective MMTV sequence (unit I) or specifically the 3' half of the nondefective proviruses (units II and III). (20 Refs)

2. CELLULAR MOLONEY MURINE SARCOMA (C-MOS) SEQUENCES ARE HYPERMETHYLATED AND TRANSCRIPTIONALLY SILENT IN NORMAL AND TRANSFORMED RODENT CELLS.

Gattoni S, Kirschmeier P, Weinstein IB, Escobedo J, Dina D
Div. Environmental Sciences, Inst. Cancer Res., Columbia Univ., New York, NY, 10032
Mol Cell Biol; 2(1):42-51 1982

The extent of methylation of the oncogenic v-mos sequence of Moloney murine sarcoma virus and its homologue present in normal cells of various vertebrate species (c-mos) was investigated. Results indicated that normal development and differentiation, prolonged serial passage, or transformation (either spontaneous or induced by radiation, chemical carcinogens, or polyoma virus) are not associated with gross rearrangements of the endogenous c-mos sequences in cellular DNA. The c-mos sequence does not contain any intervening sequences and is practically identical to the v-mos sequence. C-mos was not transcribed into RNA in any cells studied. These studies do not rule out the possibility that transient expression of c-mos sequences did occur during early transformation, or that other cellular oncogenic genes might play a role in cell transformation induced by chemical carcinogens or radiation. (43 Refs)

3. HUMAN-TUMOR-DERIVED CELL LINES CONTAIN COMMON AND DIFFERENT TRANSFORMING GENES.

Perucho M, Goldfarb M, Shimizu K, Lama C, Fogh J, Wigler M
Cold Spring Harbor Lab., Cold Spring Harbor, NY, 11724
Cell; 27(3):467-476 1981

We have screened different cultured cell lines established from human tumors for the ability of their DNAs to induce transformed foci in NIH/3T3 cells. Based on restriction endonuclease digestions and the presence of human sequences in mouse transformants, we conclude that five of these human tumor cell lines contain a gene or genes capable of transforming mouse cells and that at least three different transforming genes are present in these five lines. Three cell lines, two derived from lung carcinomas and one derived from a colon carcinoma, transfer the same or closely related human genes. If these transforming genes are mediating the tumorigenic state of the human cells, then our results indicate that overlapping pathways leading to tumorigenesis may arise independently. (Author abstract) (32 Refs)

4. HIGH-FREQUENCY COTRANSFER OF THE TRANSFORMED PHENOTYPE AND A TUMOR-SPECIFIC TRANSPLANTATION ANTIGEN BY DNA FROM THE 3-METHYLCHOLANTHRENE-INDUCED METH A SARCOMA OF BALB/C MICE.

Hopkins N, Besmer P, DeLeo AB, Law LW
Center Cancer Res., Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA, 02139
Proc Natl Acad Sci USA; 78(12):7555-7559 1981

We transformed BALB/3T3 mouse cells with cellular DNA extracted from the Meth A sarcoma, a 3-methylcholanthrene-induced tumor of BALB/c mice, and asked whether foci arising in the transfection possess the previously defined Meth A tumor-specific transplantation antigen (TSTA). Five of eight foci selected from one experiment possessed Meth A TSTA. DNA extracted from one of the five TSTA-positive clones was used in secondary rounds of transfection transformation. Four out of five foci tested from the secondary transfections possessed Meth A TSTA. These results suggest that in the Meth A sarcoma a transforming gene and a genetic determinant of TSTA are intimately related: they may be identical or very closely linked; alternatively, a particular transforming gene might induce the expression of a particular TSTA. Another possible explanation for these results is that the cotransfer of certain cellular genes by DNA transfection is considerably higher than predicted from the limited studies presently available. (Author abstract) (26 Refs)

5. ORGANIZATION AND EXPRESSION OF ENDOGENOUS VIRUS-LIKE (VL30) DNA SEQUENCES IN NONTRANSFORMED AND CHEMICALLY TRANSFORMED MOUSE EMBRYO CELLS IN CULTURE.

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Cancer Res; 42(2):569-576 1982

A cloned mouse DNA fragment containing an endogenous 'virus-like' DNA (VL30 DNA) sequence was identified by virtue of its ability to hybridize to the virus-like RNA component of mixed-pseudotype AKR-murine leukemia virus virions, its lack of detectable sequence homology with cloned AKR-murine leukemia virus DNA, and its hybridization to a 5.6 kilobase pair (30S) cellular polyadenylic acid [poly(A)]-containing RNA species. Restriction enzyme mapping of the cloned mouse fragment revealed the presence of a 5-to 6-kilobase pair VL30 DNA segment flanked by non-VL30 segments of approx 7 and 0.3 kilobase pairs. Southern blot analysis of VL30 DNA sequence organization in the DNA of two nontransformed mouse cell lines (AKR-2B, C3H/10T1/2) and two chemically transformed derivatives (AKR-MCA, C3H/MCA-58) revealed 15 to 20 bands organized in an apparent strain-specific pattern. Within a given strain, however, no differences were detectable between the nontransformed cells and their chemically transformed counterparts. The expression of VL30 genes in the above cell lines was assayed by hybridization of 32P-labeled poly(A)-containing polysomal RNA to several internal restriction fragments derived from the cloned VL30 DNA sequence. The level of VL30 RNA was enhanced approx 10-fold in both chemically transformed cell lines as compared to the nontransformed cell lines (under normal growth conditions). In addition, nontransformed AKR-2B cells maintained in the presence of purified epidermal growth factor exhibited similarly enhanced levels of VL30 RNA sequences in polysomal RNA. Since these cells display several growth characteristics of transformed cells but, in an epidermal growth factor-dependent and completely reversible fashion, these data suggest that the expression of VL30 genes is not simply incidental to chemically transformed cells but may be related to alterations in growth control. (Author abstract) (34 Refs)

6. CELLULAR GENES ANALOGOUS TO RETROVIRAL ONC GENES ARE TRANSCRIBED IN HUMAN TUMOUR CELLS.

Eva A, Robbins KC, Andersen PR, Srinivasan A, Tronick SR, Reddy P, Ellmore NW, Galen AT, Lautenberger JA, Papas TS, Westin EH, Wong-Staal F, Gallo RC, Aaronson SA
Lab. Cellular and Molecular Biology, NCI, NIH, Bethesda, MD, 20205
Nature; 295(5845):116-119 1982

Polyadenylated RNAs of certain human tumor cell lines are shown to contain transcripts related to the cell-derived transforming onc genes of molecularly cloned primate, murine or avian transforming retrovirus genomes. Thus, analogues of retroviral transforming genes are both present and frequently expressed in human neoplastic cells. (Author abstract) (52 Refs)

7. INTEGRATION SITE OF POLYOMA VIRUS DNA IN THE INDUCIBLE LPT LINE OF POLYOMA-TRANSFORMED RAT CELLS.

Mendelsohn E, Baran N, Neer A, Manor H
Dept. Biology, Technion-Israel Inst. Technology, Haifa, Israel
J Virol; 41(1):192-209 1982

The structure of polyoma virus (Py) integration site in the inducible LPT line of Py-transformed rat cells was determined by biochemical methods of gene mapping. The data indicate that LPT cultures contain Py insertions of various lengths integrated into the same chromosomal site in all the cells. The length heterogeneity of the viral insertions is due to the presence of 0, 1, 2, 3... Py genomes arranged in a direct tandem repeat within invariable sequences of viral DNA. Double-digestion experiments were also carried out with the above enzymes and with enzymes that cleave the Py genome at multiple sites. The data obtained in these experiments were used to construct a physical map of the integration site. This map showed that the early region of the virus remained intact even in the smallest insertion (which contains no whole duplicated genomes), whereas the late region was partially duplicated and split during integration. The smallest insertion is colinear with the Py physical map over a region including the entire Py genome and at least a part of the duplicated segment. This structure could give rise to nondefective circular viral DNA molecules by single homologous recombination events. Similar recombination events may occur at a higher frequency in the longer insertions, which include longer regions of homology, and may yield many more free viral genomes. The presence of these insertions in LPT cells could thus by one of the factors which account for the high inducibility of the LPT line. (34 Refs)

8. PROPOSAL FOR NAMING HOST CELL-DERIVED INSERTS IN RETROVIRUS GENOMES.

Coffin JM, Varmus HE, Bishop JM, Essex M, Hardy WD, Martin GS, Rosenberg NE, Scolnick EM, Weinberg RA, Vogt PK
(c/o Vogt) Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
J Virol; 40(3):953-957 1981

We propose a system for naming inserted sequences in transforming retroviruses (ie, onc genes), based on using trivial names derived from a prototype strain of virus. (Author abstract) (54 Refs)

9. MCDONOUGH FELINE SARCOMA VIRUS: CHARACTERIZATION OF THE MOLECULARLY CLONED PROVIRUS AND ITS FELINE ONCOGENE (V-FMS).

Donner L, Fedele LA, Garon CF, Anderson SJ, Sherr CJ
(c/o Sherr) Viral Pathology Section, NCI, Bethesda, MD, 20205
J Virol; 41(2):489-500 1982

The genetic structure of the McDonough strain of feline sarcoma virus (SM-FeSV) was deduced by analysis of molecularly cloned, transforming proviral DNA. The 8.2-kilobase pair SM-FeSV provirus is longer than those of other feline sarcoma viruses and contains a transforming gene (v-fms) flanked by sequences derived from feline leukemia virus. The order of genes with respect to viral RNA is 5'-gag-fms-env-3', in which the entire feline leukemia virus env gene and an almost complete gag sequence are represented. The complexity of the v-fms gene (3.1 +-0.3 kilobase pairs) is approximately two-fold greater than the viral oncogene sequences (v-fes) of Snyder-Theilen and Gardner-Arnstein FeSV. By heteroduplex, restriction enzyme, and nucleic acid hybridization analyses, v-fms and v-fes sequences showed no detectable homology to one another. Radiolabeled DNA fragments representing portions of the two viral oncogenes hybridized to different EcoRI and HindIII fragments of normal cat cellular DNA. Cellular sequences related to v-fms (designated c-fms) were much more complex than c-fes and were distributed segmentally over more than 40 kilobase pairs in cat DNA. Comparative structural studies of the molecularly cloned proviruses of Snyder-Theilen, Gardner-Arnstein, and SM-FeSV showed that a region of the feline leukemia virus genome derived from the pol-env junction is represented adjacent to v-onc sequences in each FeSV strain and may have provided sequences preferred for recombination with cellular genes. (Author abstract) (55 Refs)

10. CHARACTERIZATION OF RETICULOENDOTHELIOSIS VIRUS STRAIN T DNA AND ISOLATION OF A NOVEL VARIANT OF RETICULOENDOTHELIOSIS VIRUS STRAIN T BY MOLECULAR CLONING.

Chen IS, Mak TW, O'Rear JJ, Temin HM
McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706
J Virol; 40(3):800-811 1981

Reticuloendotheliosis virus strain T (REV-T) is a highly oncogenic avian retrovirus which causes a rapid neoplastic disease of the lymphoreticular system. Upon infection, this virus gives rise to two species of unintegrated linear viral DNA, which are 8.3 and 5.5 kilobase pairs long and represent the helper virus (REV-A) and the oncogenic component (REV-T), respectively. Restriction endonuclease cleavage maps of these two DNA components indicate that REV-T DNA has a large portion of the genome deleted with respect to REV-A DNA and a substitution about 0.8 to 1.5 kilobase pairs long that is unrelated to REV-A DNA. These additional sequences comprise the putative transforming region of REV-T (rel). A chicken spleen cell line transformed by REV-T produced virus which upon infection gives rise to three species of unintegrated linear viral DNA (8.3, 5.5, and 3.3 kilobase pairs). We isolated the proviruses of the 8.3-and 3.3-kilobase pair species from this cell line by cloning in the phage vector Charon 4A. Restriction enzyme mapping showed that the two proviral clones are proviruses of REV-A and a variant of REV-T, respectively. A subclone of the variant REV-T provirus specific for the rel sequences of REV-T was used as a hybridization probe to demonstrate that the rel sequences are different from the putative transforming sequences of Schmidt-Ruppin Rous sarcoma virus strain A, avian myelocytomatosis virus, avian myeloblastosis virus, avian erythroblastosis virus, Abelson murine leukemia virus, and Friend erythroleukemia virus. In addition, the rel-specific hybridization probe was used to identify a specific set of sequences which are present in uninfected avian DNAs digested with several restriction enzymes. The corresponding cell sequences are not arranged like rel in REV-T. (Author abstract) (46 Refs)

11. COMPARATIVE RESTRICTION ENDONUCLEASE MAPS OF PROVIRAL DNA OF THE PRIMATE TYPE C SIMIAN SARCOMA-ASSOCIATED VIRUS AND GIBBON APE LEUKEMIA VIRUS GROUP.

Trainor CD, Wong-Staal F, Reitz MS
(c/o Reitz) Div. Cancer Treatment, Lab. Tumor Cell Biology, NCI, Bethesda, MD, 2 0205
J Virol; 41(1):298-308 1982

Extrachromosomal DNA was purified from canine thymus cells acutely infected with different strains of infectious primate type C viruses of the woolly monkey (simian) sarcoma helper virus and gibbon ape leukemia virus group. All DNA preparations contained linear proviral molecules of 9.1 to 9.2 kilobases, at least some of which represent complete infectious proviral DNA. Cells infected with a replication-defective fibroblast-transforming sarcoma virus and its helper, a replication-competent nontransforming helper virus, also contained a 6.6-to 6.7-kilobase DNA. These proviral DNA molecules were digested with different restriction endonucleases, and the resultant fragments were oriented to the viral RNA by a combination of partial digestions, codigestion with more than one endonuclease, digestion of integrated proviral DNA, and hybridization with 3'-and 5'-specific viral probes. The 3'- and 5'-specific probes each hybridized to fragments from both ends of proviral DNA, indicating that, in common with those of other retroviruses, these proviruses contain a large terminal redundancy at both ends, each of which consists of sequences derived from both the 3' and 5' regions of the viral RNA. The proviral sequences are organized 3',5'-unique-3',5'. Four restriction enzymes (KpnI, SmaI, PstI, and SstI) recognized sites within the large terminal redundancies, and these sites were conserved within all the isolates tested. This suggests that both the 3' and 5' ends of the genomic RNA of these viruses are extremely closely related. In contrast, the restriction sites within the unique portion of the provirus were not strongly conserved within this group of viruses, even though they were related along most of their genomes. Whereas the 5' 60 to 70% of the RNA of these viruses was more closely related by liquid hybridization experiments than was the 3' 30 to 40%, restriction sites within this region were not preferentially conserved, suggesting that small sequence differences or point mutations or both exist throughout the entire unique portion of the genome among these viruses. (Author abstract) (37 Refs)

12. MAPPING OF NONCONDITIONAL AND CONDITIONAL MUTANTS IN THE SRC GENE OF PRAGUE STRAIN ROUS SARCOMA VIRUS.

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Virology; 116(1):72-83 1982

Restriction endonuclease EcoRI digestion of the viral DNA of 12 nonconditional transformation defective (td) mutants of Prague strain Rous sarcoma virus (PR-RSV) has divided these mutants into two groups. Five mutants possess an EcoRI B (src gene-containing) fragment of the same size as that from wild type PR-RSV and thus these mutants have no detectable diminution in the transforming src gene. The other 7 mutants bear deletions of 1.0 to 1.8 kilobases in the 3.2-kilobase EcoRI B fragment. The extents of these deletions have been mapped using a number of restriction endonucleases and by comparing these results with studies on the nucleotide sequence of src we conclude that the td mutants have deleted sequences at the 5' end of src, and in some cases also in regions between src and env, leaving intact at least some 3' src sequences. These td mutants recombine in differing patterns with 14 temperature-sensitive (ts) src gene mutants. This enables many of the ts mutations to be localized in limited regions of src, 10 of them being clustered in the 3' 40% of the gene the remaining four bearing at least one mutation in the 5' 60% of src. A nonconditional src gene mutant that transforms cells to a fusiform as opposed to round cell morphology (td SF/LO 104) also possesses a lesion that maps in the 5' 60% of the src gene. (Author abstract) (28 Refs)

13. AVIAN MYELOBLASTOSIS VIRUS TRANSFORMING GENE IS RELATED TO UNIQUE CHICKEN DNA REGIONS SEPARATED BY AT LEAST ONE INTERVENING SEQUENCE.

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J Virol; 41(1):250-257 1982

Identification of several additional restriction endonuclease sites within the cellular substitution (amv) inserted into the avian myeloblastosis virus proviral genome has permitted us to isolate different regions of the amv sequence. These subsets of the avian myeloblastosis virus transforming gene have been cloned in the plasmid pBR322 and used as hybridization probes to investigate the topology of homologous (proto-amv) normal chicken DNA sequences. The results showed that the cellular proto-amv sequences in C/O chicken DNA are interrupted by at least one intervening sequence. A partial arrangement of the proto-amv sequences is presented. (Author abstract) (32 Refs)

14. CELL ONCOGENES ARE LOCATED ON THE LARGE MICROCHROMOSOMES IN CHICKEN CELLS.

Tereba A, Lai MM
Div. Virology, St. Jude Children's Res. Hosp., Memphis, TN, 38101
Virology; 116(2):654-657 1982

The chromosomal locations of c-myc and c-myb, the cell homologs of the transforming genes present in myelocytomatosis virus 29, MC29, and avian myeloblastosis virus, AMV, respectively, were determined in White Leghorn chickens using in situ hybridization. Nucleic acid probes containing MC29 and AMV-RNAs were used to localize both c-myc and c-myb to a subset of large microchromosomes. The chromosomal location of c-myc was confirmed using nucleic acid probes containing RNA from MH-2, which also contains a myc-like sequence, and cloned DNA containing the chicken c-myc gene. In conjunction with our previous results localizing c-src and c-erb, we have demonstrated that several cell oncogene homologs appear to be localized on a subset of large microchromosomes. (Author abstract) (18 Refs)

15. PERSISTENCE AND EXPRESSION OF MAREK'S DISEASE VIRUS DNA IN TUMOUR CELLS AND PERIPHERAL NERVES STUDIED BY IN SITU HYBRIDIZATION.

Ross NL, DeLorbe W, Varmus HE, Bishop JM, Brahic M, Haase A
Houghton Poultry Res. Station, Houghton, Huntingdon PE17 2DA, England
J Gen Virol; 57(part2):285-296 1981

We have used cloned fragments of Marek's disease virus (MDV) DNA and in situ hybridization to search for virus DNA and study its expression in infected chick embryo fibroblasts (CEF), lymphoblastoid cell lines, tumors and neural lesions. DNA from the HPRS 16/att strain of MDV was cleaved with EcoRI endonuclease and several fragments were cloned in Escherichia coli using the vector PBR322. Seven fragments ranging in size from 2.6 to 11 kbp representing approx. 25% of the MDV genome were labelled in vitro and annealed to EcoRI digests of DNA from infected cells and tumors following separation and transfer according to the Southern blotting procedure. Most of the selected MDV DNA fragments hybridized to fragments of corresponding sizes in EcoRI digests of DNA from cell lines and tumors and failed to hybridize to digests of uninfected chick cell DNA. In situ hybridization using 3H-labelled DNA with specific activity of 10(8) d/min/ug as a probe showed intranuclear MDV DNA in infected CEF, in every cell of two lymphoblastoid cell lines and in the majority of infiltrating or proliferating lymphoid cells found in Type 'A' lesions of grossly enlarged peripheral nerves. Both intranuclear and cytoplasmic RNA were detected in cells that contained virus DNA. However, comparatively little virus RNA appears to be transcribed in cell lines and in infected tissues from the regions of virus DNA (25% of genome) used as probe in this study. Our results favor the hypothesis that the accumulation of lymphoid cells in nerves is not the result of an inflammatory response to infected nerve cells but is rather the consequence of proliferating transformed cells. (Author abstract) (28 Refs)

TRANSFORMATION GENE EXPRESSION AND REGULATION

16. GLUCOCORTICOID REGULATION OF THE HA-MUSV P21 GENE CONFERRED BY SEQUENCES FROM MOUSE MAMMARY TUMOR VIRUS.

Huang AL, Ostrowski MC, Berard D, Hager GL
Lab. Tumor Virus Genetics, NCI, Bethesda, MD, 20205
Cell; 27(2):245-255 1981

Molecular chimeras with the p21 transforming gene of Harvey murine sarcoma virus linked to DNA containing the long terminal repeat (LTR) of mouse mammary tumor virus (MMTV) have been constructed. Transformants of NIH 3T3 cells induced by transfection with MMTV LTR-p21 hybrid DNA have been identified that express the normal p21 gene product. The levels of p21 RNA and protein in these transformants are regulated by physiological concentrations of dexamethasone, a synthetic glucocorticoid hormone. Hybrid transcripts containing p21 gene sequences originate at the normal MMTV viral initiation site. It is concluded that sequences necessary for hormonal control of transcription are completely specified by the viral genome and probably map within the viral LTR. (Author abstract) (45 Refs)

17. STRUCTURE AND PHOSPHORYLATION OF THE FUJINAMI SARCOMA VIRUS GENE PRODUCT.

Pawson T, Kung TH, Martin GS
Dept. Microbiology, Univ. British Columbia, Vancounver, British Columbia V6T 1W5, Canada
J Virol; 40(3):665-672 1981

The Fujinami avian sarcoma virus (FSV) transforming gene product, P140, is a fusion protein which contains both gag-related and FSV-specific methionine-containing tryptic peptides. The virion protease p15 cleaved P140 into two fragments: an N-terminal 33K fragment which contained all but one of the gag-related tryptic peptides and a C-terminal 120K fragment which contained all of the FSV-specific tryptic peptides. The 33K gag-related fragment from P140 phosphorylated in FSV-transformed cells contained only phosphoserine, whereas the 120K C-terminal FSV-specific fragment contained both phosphoserine and phosphotyrosine. P140 isolated from cells infected at the nonpermissive temperature with an isolate of FSV which is temperature sensitive for transformation had a normally phosphorylated 33K fragment, but a hypophosphorylated 120K fragment deficient in both phosphotyrosine and phosphoserine. When P140 was immunoprecipitated from cells and phosphorylated in vitro at tyrosine residues in the immune complex kinase reaction, only the FSV-specific fragment was labeled. These data define the structure of FSV P140 and locate the phosphorylated amino acids within the two regions of the polypeptide. (Author abstract) (15 Refs)

18. ROUS SARCOMA VIRUS-INDUCED PHOSPHORYLATION OF A 50,000-MOLECULAR WEIGHT CELLULAR PROTEIN.

Brugge JS, Darrow D
Dept. Microbiology, State Univ. New York at Stony Brook, Stony Brook, NY, 11794
Nature; 295(5846):250-253 1982

Studies were performed to determine whether the 50,000-mol wt phosphotyrosine-containing protein pp50 is present in uninfected cells and whether phosphorylation of pp50 at tyrosine depends on Rous sarcoma virus (RSV)-induced transformation. Using serum from tumor-bearing rabbits (TBR), pp50 was immunoprecipitated from 32P-labeled chicken cells transformed by the SR-A strain of RSV. Comparison of the two-dimensional gel patterns of uninfected cell phosphoproteins with a mixture of the TBR immunoprecipitate and uninfected cell phosphoproteins indicated that the pp50 which is bound to the single virus-encoded polypeptide pp60src and precipitated RSV-transformed cells migrate just to the acidic side of pp50 present in uninfected cells. Results indicate that the phosphoserine-containing form of pp50 is present in uninfected chicken cells; on transformation by RSV, a second form of pp50 detectable by two-dimensional analysis of 32P-labeled proteins contains phosphotyrosine as well as phosphoserine. The phosphorylation of pp50 at tyrosine is not temperature-sensitive (TS) in cells infected with mutant viruses containing a TS defect in the src gene. The temperature stability might result from the strong interaction between the mutant pp60src protein and pp50. (25 Refs)

19. SYNTHETIC PEPTIDE FRAGMENT OF SRC GENE PRODUCT INHIBITS THE SRC PROTEIN KINASE AND CROSSREACTS IMMUNOLOGICALLY WITH AVIAN ONC KINASES AND CELLULAR PHOSPHOPROTEINS.

Wong TW, Goldberg AR
Rockefeller Univ., New York, NY, 10021
Proc Natl Acad Sci USA; 78(12):7412-7416 1981

All the known avian sarcoma viruses have associated protein kinase activities that phosphorylate tyrosine residues of their target proteins. A decapeptide fragment of pp60src of Rous sarcoma virus (RSV), residues 415-425, and an analog of that sequence have been chemically synthesized by solid-phase methods. The two decapeptides were not phosphorylated by pp60src of RSV, P90 of Y73 avian sarcoma virus, or P140 of Fujinami sarcoma virus. However, both peptides were able to inhibit competitively the kinase activities associated with the transforming proteins. Antiserum was raised against one of the peptides and IgG was purified from the serum by affinity chromatography. The antibody was able to precipitate pp60src of RSV as well as P90 of Y73 virus from cells infected with these viruses. The antibody also precipitated a number of high molecular weight phosphoproteins from normal chicken and rat fibroblasts and from several lines of virus-transformed cells. (Author abstract) (29 Refs)

20. GENE PRODUCTS OF MCDONOUGH FELINE SARCOMA VIRUS HAVE AN IN VITRO-ASSOCIATED PROTEIN KINASE THAT PHOSPHORYLATES TYROSINE RESIDUES: LACK OF DETECTION OF THIS ENZYMATIC ACTIVITY IN VIVO.

Barbacid M, Lauver AV
Lab. Cellular and Molecular Biology, NCI, Bethesda, MD, 20205
J Virol; 40(3):812-821 1981

The primary translational product of the McDonough (SM) strain of feline sarcoma virus (FeSV) is a 180,000-dalton molecule, SM P180, that contains the p15-p12-p30 region of the FeLV gag gene-coded precursor protein and a sarcoma virus-specific polypeptide. In addition, cells transformed by SM-FeSV express a 120,000-dalton molecule, SM P120, that is highly related to the non-helper virus domain of SM P180. Both SM-FeSV gene products were found to be intimately associated with the membrane fraction of SM-FeSV-transformed cells. Immunoprecipitates containing SM P180 and SM P120 exhibited a protein kinase activity capable of phosphorylating tyrosine residues of both viral gene products but not immune immunoglobulin G molecules. By independently immunoprecipitating each of the two SM-FeSV proteins we found that most of the tyrosine-specific phosphorylating activity was associated with the SM P120 molecule. In vivo analysis of 32P-labeled SM P180 and SM P120 revealed their phosphoprotein nature; however, both molecules exhibited low levels of phosphorylation and did not contain phosphotyrosine residues. Finally, we did not detect any significant elevation in the levels of phosphotyrosine in the protein fraction of SM-FeSV transformants. Thus, if SM-FeSV were to induce malignant transformation by a mechanism involving phosphorylation of tyrosine residues, the viral gene products must interact with a small subset of cellular proteins that do not represent a significant fraction of the total cellular protein content. (Author abstract) (44 Refs)

21. TRANSFORMATION-DEFECTIVE MUTANT OF ADENOVIRUS TYPE 5 CONTAINING A SINGLE ALTERED E1A MRNA SPECIES.

Carlock LR, Jones NC
Dept. Biological Sciences, Purdue Univ., West Lafayette, IN, 47907
J Virol; 40(3):657-664 1981

A mutant of adenovirus type 5 containing an octanucleotide insert in region E1a of the viral genome was constructed. The insert was present in only one (13s) of the three overlapping mRNA's synthesized from this region. The insert was within the sequences removed by RNA splicing during the production of the other two mRNA's. The insertion resulted in a shift in the translational reading frame of the 13s mRNA and the probable premature termination of translation. The mutant was defective for viral DNA replication in HeLa cells and the transformation of rat embryo and baby rat kidney cells, indicating that a product encoded by the 13s mRNA is required for these two processes. Other early regions of the genome were expressed in HeLa cells infected by this mutant although in some cases the expression was decreased as compared with wild-type-infected cells. (Author abstract) (27 Refs)

22. TRYPTIC AND CHYMOTRYPTIC METHIONINE PEPTIDE ANALYSIS OF THE IN VITRO TRANSLATION PRODUCTS SPECIFIED BY THE TRANSFORMING REGION OF ADENOVIRUS TYPE 2.

Halbert DN, Raskas HJ
Dept. Microbiology, Health Sciences Center, State Univ. New York at Stony Brook, Stony Brook, NY, 11794
Virology; 116(2):406-418 1982

Early region 1 (E1) cytoplasmic RNAs of adenovirus Type 2 were translated in vitro. Structural relationships between these proteins were then established by tryptic and chymotryptic digestion and two-dimensional peptide mapping. This analysis also allowed a direct comparison of these proteins with polypeptides isolated from early infected cell extracts and previously assigned to E1 by indirect means. E1a (0-4.5%) RNA encodes five proteins in vitro: 35K, 41K, 47K and 53K at early times, and a 28K protein at later times in infection. These five proteins are all highly related by peptide mapping analysis, and are also related to a group of four proteins isolated from cell extracts prepared early in infection. E1b (4.5-11.0%) early RNA encodes 52K and one or more 15K proteins in vitro. The 52K protein shares tryptic peptides with a 53K immunoprecipitated T antigen. A 15K protein shares some peptides with the 52K protein and with several proteins isolated from infected cells. At intermediate to late times, E1b RNA encodes a 12K protein that corresponds to the virion structural polypeptide IX. These data also permit the correlation of E1 proteins synthesized in vitro with the polypeptides predicted by E1 sequence analysis. (Author abstract) (45 Refs)

23. IDENTIFICATION OF A 39,000-DALTON PROTEIN IN CELLS TRANSFORMED BY THE FBJ MURINE OSTEOSARCOMA VIRUS.

Curran T, Teich NM
Imperial Cancer Res. Fund Lab., Lincoln's Inn Fields, London WC2A 3PX, England
Virology; 116(1):221-235 1982

Two components of the FBJ murine osteosarcoma virus complex have been isolated separately in tissue culture; the FBJ murine leukemia virus (FBJ-MLV) by dilution and the FBJ murine sarcoma virus (FBJ-MSV) by the establishment of nonproducer transformed rat cells. Analysis of these cells using MLV antisera indicated that there were no new proteins related to viral structural proteins specifically associated with the presence of the FBJ-MSV genome. The FBJ-MSV nonproducer cells were used to induce tumors in syngeneic and allogeneic F1 rats. Sera from tumor-bearing rats were examined for activity against FBJ-MSV-specific antigens. A number of sera were found to precipitate a 39,000-dalton protein, p39, from several producer and nonproducer FBJ-MSV transformed rodent cells, but not from cells transformed by other strains of MSV or cells infected with MLV. Precipitation of p39 was not blocked by the presence of excess viral proteins, indicating that p39 is not related to the viral structural proteins. This conclusion was confirmed by methionine tryptic peptide analysis which showed that the fingerprint of p39 was distinct from those of the viral gag or env gene proteins. The data demonstrate the presence of a unique antigenic protein, unrelated to the MLV proteins, in FBJ-MSV transformed cells. (Author abstract) (41 Refs)

24. LETHAL EFFECT OF THE ABELSON MURINE LEUKEMIA VIRUS TRANSFORMING GENE PRODUCT.

Ziegler SF, Whitlock CA, Goff SP, Gifford A, Witte ON
Molecular Biology Inst., Dept. Microbiology, Univ. California Los Angeles, Los Angeles, CA, 90024
Cell; 27(3):477-486 1981

Infection of NIH/3T3 and Balb/c/3T3 fibroblastic cell lines by Abelson virus results in stable transformation in most cases. We have observed that certain rodent cell lines, including some Balb/c/3T3 sublines, do not maintain stable transformation following infection. Within 3 to 4 wk of infection of these cell lines a large fraction of the cells is not recoverable upon serial passage and appear to be killed. The residual population of cells displays a flat, nontransformed phenotype. Concomitant with this reversion is the loss of the integrated provirus and loss of expression of the Abelson virus transforming protein. This loss of the integrated provirus is specific to transformation-competent viral strains. The effect of Abelson virus on these cells appears to be, in part, due to a lethal effect of the transforming protein on the cells. We have selectively isolated mutants of Abelson virus that stably transformed these rodent cell lines without expressing a lethal effect. Analysis of the nucleic acid and protein structure of these mutant virus strains showed that the transforming proteins are shorter, having lost expression of the carboxy-terminal one-third of the protein. We suspect that the carboxy-terminal portion of the wild-type Abelson protein may modulate the in vivo expression of the protein kinase activity and that this may cause the transforming protein to have a deleterious effect on certain cell lines. (Author abstract) (33 Refs)

25. GENETIC ANALYSIS OF TUMORIGENESIS: IX SUPPRESSION OF ANCHORAGE INDEPENDENCE IN HYBRIDS BETWEEN TRANSFORMED HAMSTER CELL LINES.

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Div. Cell and Molecular Biology, Chester Beatty Res. Inst., Inst. Cancer Res.: Royal Cancer Hosp., Fulham Road, London SW3 6JB, England
Somatic Cell Genet; 7(6):713-723 1981

One characteristic of the transformed phenotype, expression of anchorage independence, was examined in hybrids between different anchorage-independent Chinese hamster fibroblasts. Three anchorage-independent (AID) cell lines were assayed to see whether the AID phenotype was suppressed by fusion to anchorage-dependent nontumorigenic CHEF/18 cells. In each case the AID phenotype was suppressed by fusion to an appropriately marked CHEF/18. To examine whether the same genomic changes conferring anchorage independence had occurred in tumorigenic CHEF/16 and in seven AID cell lines of independent origin, the cells were fused to various biochemically marked derivatives of CHEF/16. Two cell lines, 294-7MC3/10 and Chec1T2MC6, gave rise to AID hybrids when fused to CHEF/16 cells. The absence of complementation suggests that 294-7MC3/10, Chec1T2MC6, and CHEF/16 have the same change leading to anchorage independence. Complementation between different AID cell lines suggests that genomic changes leading to anchorage independence in CHEF/16 are not the same as the changes in the five CHEF/18 mutants. Results are showing that there are at least two alternative genomic changes by which Chinese hamster fibroblasts can become anchorage independent. (23 Refs)

EXPERIMENTAL MODULATION OF ONCOGENIC TRANSFORMATION

26. MOUSE EMBRYONIC TRANSFORMING GROWTH FACTORS RELATED TO THOSE ISOLATED FROM TUMOR CELLS.

Twardzik DR, Ranchalis JE, Todaro GJ
Lab. Viral Carcinogenesis, NCI, Frederick, MD, 21701
Cancer Res; 42(2):590-593 1982

Growth factors with the two characteristic properties of sarcoma growth factor, the ability to stimulate anchorage-independent growth of normal mouse or rat fibroblasts and the ability to compete with 125I-labeled epidermal growth factor for receptor binding, can be isolated from 12-to 13-day-old normal mouse embryos of various strains. Two size classes of the transforming factor from embryo cells can be isolated with apparent mol wt of 20,000 and 10,000. The lower-mol-wt factor has been purified several hundred-fold and has the same properties as the peptide with a mol wt of 10,000 produced by mouse sarcoma virus-transformed 3T3 cells. Whole-mouse embryos contain approx 10% as much sarcoma growth factor per g of tissue as do the murine sarcoma virus-transformed cells; how it is distributed among the embryonic tissues remains to be determined. (Author abstract) (14 Refs)

27. DECREASED TUMORIGENICITY OF RODENT CELLS AFTER FUSION WITH LEUKOCYTES FROM NORMAL AND LEUKEMIC DONORS.

Geurts van Kessel AH, De Boer WC, Van Agthoven AJ, Hagemeijer A
Dept. Cell Biology and Genetics, Erasmus Univ., Rotterdam, The Netherlands
Somatic Cell Genet; 7(6):645-656 1981

Hybrid cell lines, derived from fusion of tumorigenic rodent cells (mouse Pg 19 or Chinese hamster a3) with WBC from leukemic donors were isolated and tested for growth in congenitally athymic nude mice. Cytogenetic analysis, using banding techniques, was performed on cells before injection and on the tumors which eventually developed. Pg 19 mouse cells alone were highly tumorigenic; 1 x 10(5) cells resulted in 100% tumors. The a3 grew more slowly and 2 x 10(6) cells were needed to produce tumors in 75% of mice in 10 days. WBC from chronic myeloid leukemia donors, with inocula of up to 4 x 10(7) cells, failed to form tumors within 3 mo in nude mice, further immunosuppressed by ip cyclophosphamide. The chromosome analyses did not reveal a human chromosome-bearing factor(s) which singly appeared responsible for the tumor suppression. The presence of the Philadelphia translocation in the leukemic cells does not appear to have deprived these cells of their tumor-suppressing ability. (29 Refs)

28. HUMAN CELL HYBRIDS: ANALYSIS OF TRANSFORMATION AND TUMORIGENICITY.

Stanbridge EJ, Der CJ, Doersen CJ, Nishimi RY, Peehl DM, Weissman BE, Wilkinson JE

Dept. Microbiology, Coll. Medicine, Univ. California, Irvine, CA, 92717

Science; 215(4530):252-259 1982

Intraspecific human-human cell hybrids provide a stable model system with which to investigate the genetic control of transformed and tumorigenic phenotypes. Using this system it has been shown that these phenotypes are under separate genetic control. Furthermore, the tumorigenic phenotype can be complemented by fusion of different tumorigenic cells, resulting in nontumorigenic hybrids. This system also provides information on the control of differentiated function. Molecular cytogenetic techniques should reveal the nature of the chromosomal control of neoplastic transformation. (Author abstract) (47 Refs)

29. MULTISTEP ORIGIN OF TUMOR-FORMING ABILITY IN CHINESE HAMSTER EMBRYO FIBROBLAST CELLS.

Smith BL, Sager R

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Cancer Res; 42(2):389-396 1982

Twenty-one anchorage-independent subclones and 10 subclones with reduced serum requirements were isolated as single-step mutants spontaneously or after ethylmethanesulfonate or N-methyl-N'-nitro-N-nitrosoguanidine mutagenesis of CHEF/18 diploid Chinese hamster embryo fibroblasts. Anchorage-independent mutants retain the high serum requirement and nontransformed morphology typical of CHEF/18. Only four of 21 anchorage mutants have spontaneously produced tumors when injected at 10(7)/site in nude mice, and these were only at a fraction of sites. Low-serum (LS) mutants acquire transformed morphology and increased anchorage-independent growth simultaneously with the loss of high-serum requirement. Only 2 of 10 LS mutants have spontaneously produced tumors. However, when some anchorage and LS mutants were remutagenized and when mutagenized populations were injected into nude mice, tumors appeared at many of the injected sites. In contrast, untreated CHEF/18 cells have never given tumors (0 of 34 sites), and mutagenized CHEF/18 cells have given tumors at only 3 of 29 sites. These results demonstrate that malignant transformation is a multistep process in the Chinese hamster embryo fibroblast system. Most one-step mutants selected for anchorage independence or reduced serum requirements do not have tumor-forming potentials higher than that of the parent CHEF/18. Thus, anchorage-independent and LS phenotypes per se do not account for the increase in tumor-forming potential. It is proposed that the genomic rearrangement process as well as specific mutations may contribute to tumorigenicity. (Author abstract) (67 Refs)

30. ALTERED PROPERTIES OF TUMORS INDUCED BY ADENOVIRUS TYPE 12 DNA FRAGMENT TRANSFORMED CELLS AFTER GROWTH IN IMMUNOCOMPETENT RATS.

Moriuchi T, Yamashita T, Imamura M, Fujinaga K

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Int J Cancer; 29(1):101-105 1982

The GY1-3-1 cell line, which was derived from a rat cell line transformed by the Ad 12 HindIII-G fragment, can induce tumors in newborn rats, but not in mature rats. However, when 10 mature rats were transplanted with a large number of GY1-3-1 tumor fragments, two developed tumors with a long latency period. These two tumors (GY1-3M and GY1-3Y) were quite different in properties from the originally inoculated GY1-3-1 tumor. Tumor transplantation studies revealed that both GY1-3M and GY1-3Y tumors could grow in mature rats, and the number of takes with transplanted tumor was 100% with GY1-3M tumor and 40% with GY1-3Y tumor. Histopathologically original GY1-3-1 tumor showed a morphology of undifferentiated sarcoma, while the histologic picture of GY1-3M and GY1-3Y tumors was similar to that encountered in human fibrosarcoma and malignant fibrous histiocytoma, respectively. Both GY1-3M and GY1-3-1 tumors, when recultured in vitro, gave rise to cell lines with a fibroblastic appearance, although the original GY1-3-1 cell line exhibited an epithelioid morphology. In chromosome analysis, the GY1-3-1 cell line was pseudodiploid, while the cell lines from GY1-3M and GY1-3Y tumors were hyperdiploid or near-triploid. The metacentric marker chromosome, M1, was present in mitotic cells of the GY1-3-1 line and of the GY1-3M tumor lines, but absent from the GY1-3Y tumor lines. By Southern blot hybridization, multiple bands of cellular DNAs from parental GY1-3-1 cells hybridized with labeled Ad12 HindIII-G, while only a single band hybridized in DNAs from both GY1-3M and GY1-3Y tumors. (Author abstract) (15 Refs)

31. ALTERED PROPERTIES OF TUMORS INDUCED BY ADENOVIRUS TYPE 12 DNA FRAGMENT-TRANSFORMED CELLS AFTER IN VIVO GROWTH (MEETING ABSTRACT).

Moriuchi T, Yamashita T, Imamura M, Fujinaga K

Department of Mol Biol, Cancer Research Institute, Sapporo, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The Gy1-3-1 cell line, which was derived from a rat cell line transformed by the Ad12 HindIII-G fragment, can induce tumors in newborn rats but not in mature rats. However, tumors could be induced in mature rats by inoculation of a large amount of GY1-3-1 tumor fragments which were obtained from rats inoculated with GY1-3-1 cells as newborn. The tumors induced in immunocompetent rats markedly differred in morphology, and immunological and biological properties to originally inoculated tumors. Southern blot analysis demonstrated a great difference in the pattern of persistence of the viral sequence in cell lines before inoculation and after growth in immunocompetent rats. (no Refs)

32. TRANSFECTION OF FIBROBLASTS BY CLONED ABELSON MURINE LEUKEMIA VIRUS DNA AND RECOVERY OF TRANSMISSIBLE VIRUS BY RECOMBINATION WITH HELPER VIRUS.

Goff SP, Tabin CJ, Wang JY, Weinberg R, Baltimore D
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J Virol; 41(1):271-285 1982

A cloned, permuted DNA copy of the Abelson murine leukemia virus (A-MuLV) genome was capable of eliciting the morphological transformation of NIH/3T3 fibroblasts when applied to cells in a calcium phosphate precipitate. The efficiency of the process was extremely low, yielding approx one transformant per microgram of DNA under conditions which give 10(4) transfectants per microgram of other DNAs (eg, Moloney sarcoma virus proviral DNA). The DNA was able to induce foci, even though the 3' end of the genome was not present. The transforming gene was thus localized to the 5' portion of the genome. The transformed cells all produced viral RNA and the virus-specific P90 protein. Transmissible virus could be rescued from these cells at very low frequencies by superinfection with helper virus; the rescued A-MuLV virus had variable 3' ends apparently derived by recombination with the helper. Dimerization of the permuted A-MuLV cloned genome to reconstruct a complete provirus did not improve transformation efficiency. Virus could be rescued from the transformants, however, at a high efficiency. Cotransfection of the permuted A-MuLV DNA with proviral M-MuLV DNA yielded a significant increase in the efficiency of transformation and cotransfection of dimeric A-MuLV and proviral M-MuLV resulted in a high-efficiency transformation yielding several thousand more transformants per microgram than A-MuLV DNA alone. We propose that helper virus efficiently rescues A-MuLV from transiently transfected cells which would not otherwise have grown into foci. We hypothesize that multiple copies of A-MuLV DNA introduced into cells by transfection are toxic to cells. In support of this hypothesis, we have shown that A-MuLV DNA sequences can inhibit the stable transformation of cells by other selectable DNAs. (Author abstract) (38 Refs)

33. TRANSFORMING RNA: CONSIDERATIONS ON THE MECHANISM OF LEUKEMOGENESIS IN MICE (MEETING ABSTRACT).

Hamada K, Yanagihara K, Kajitani T, Kamiya K, Seyma T, Yokoro K
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Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Although the causative implication of a virus in induction of leukemia in mice has long been suspected, a unified concept of leukemogenic mechanism has not been wholly established, due partly to the fact that many mouse strains are naturally infected with C-type RNA retroviruses. Leukemias developed at a high rate in NIH/Swiss mice following administration of N-nitrosoethylurea (NEU). An agent, which transforms cells of several species in vitro and appears to be leukemogenic in collaboration with endogenous MuLV, was isolated from thymi of NEU-induced leukemic mice. The cell transforming capacity of the agent was completely destroyed by treatment with RNase but was not affected by DNase. RNA extracted from SC-1 mouse cells transformed by the agent also showed cell transforming ability. These findings imply that chemical or physical agents exert their leukemogenic activity through the induction of RNA molecules containing transcripts of transforming gene of the cellular origin. (no Refs)

34. TRANSFECTION OF AVIAN SARCOMA PROVIRAL DNA (MEETING ABSTRACT).

Ogura H, Fujiwara T, Yabe Y
Department of Virology, Cancer Institute Okayama University Medical School, Okayama, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The C/O chick embryo cells (CEC) were transformed by the transfection of the subgroup A, B and C avian sarcoma proviral DNA. However, the C/B CEC were not transformed by the transfection of subgroup B proviral DNA and the C/C CEC not by subgroup C proviral DNA, though the transfected cells each produced sarcoma viruses. The proviral DNA of BH-RSV, lacking env gene, did not transform any CEC tested. These results support the idea that the secondary infection of CEC with sarcoma viruses multiplying after transfection is necessary for CEC transformation. (no Refs)

35. TRANSFORMATION OF HAMSTER KIDNEY CELLS BY FRAGMENTS OF BK VIRUS DNA.

Grossi MP, Corallini A, Valieri A, Balboni PG, Poli F, Caputo A, Milanesi G, Barbanti-Brodano G
(c/o Barbanti-Brodano) Inst. Microbiology, Univ. Ferrara, 44100 Ferrara, Italy
J Virol; 41(1):319-325 1982

Hamster kidney cells were transformed, with comparable efficiency, by circular or linear molecules of complete BK virus (BKV) genome and by agarose gel-purified fragments of BKV DNA obtained by single or double digestions with various restriction endonucleases. Only fragments containing the complete early region of BKV DNA displayed transforming activity. Analysis by blot hybridization of the arrangement of viral DNA sequences in a cloned cell line transformed by a 3.8-kilobase fragment, obtained after sequential digestion of BKV DNA with HhaI and BamHI, showed the presence of seven viral integrations into the cellular DNA. Apparently all of the integrated viral molecules contained the entire early region of BKV DNA. Large T antigen, small t antigen, and the 56,000-dalton nonviral Tau antigen were detected in transformed cells by immunoprecipitation. The pattern of integration of viral sequences in transformed cells was constant over many generations. Likewise, large T antigen was always detected in transformed cells at various passage levels. These results may suggest that all of the sequences of the early region coding for large T antigen are required for transformation by BKV. Alternatively, subgenomic segments of the BKV DNA early region may be unable to transform because the appropriate polyadenylation site, necessary to obtain a complete functional transcriptional unit, is removed by the restriction enzyme cleavage. (Author abstract) (34 Refs)

36. IN VITRO DIFFERENTIATION OF CHICKEN EMBRYO SKIN CELLS TRANSFORMED BY ROUS SARCOMA VIRUS.

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J Cell Physiol; 109(3):373-385 1981

Epidermal cells isolated from 14-day chicken embryo shank skin epidermis were infected in vitro with Rous sarcoma virus (RSV). After a few wk, rapidly growing colonies of epithelial cells appeared among transformed fibroblastic cells. When isolated and subcultured, the cells possessed typical markers of skin epidermis such as major keratin and typical epithelial cell type morphology which strongly suggested they were transformed epidermal cells which retained their differentiated characteristics but had the capacity to propagate in cell culture. If cells infected with RSV tsNY68 (a mutant with a temperature lesion on the src gene) were used, similar transformed cells were obtained at the permissive temperature of 36 C, as evidenced by incorporation of 35S-methionine into keratins, demonstrated with polyacrylamide gel electrophoresis. At a nonpermissive temperature (41 C), appearance of cells changed, but additional keratin species were produced. Cells also developed a 'cornified envelope' which indicated extensive differentiation. The study indicates the src gene is essential for propagation of differentiated cells in culture, but eliminates only some of the differentiated characteristics. (34 Refs)

37. CELLULAR TRANSFORMATION BY RADIATION: INDUCTION, PROMOTION, AND INHIBITION.

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J Supramol Struct Cell Biochem; 16(4):311-336 1981

Steps and factors in radiation transformation are reviewed. Recent and current studies using mammalian cell cultures are described: subjects include oncogenic transformation (TR) of animal cells in vitro, quantitative studies in radiation TR, modification of TR by the protease inhibitor antipain, nutritional factors such as retinoids, and thyroid hormone as a modulator of carcinogenesis. Oncogenic TR of human cells in vitro is discussed. (61 Refs)

38. ENHANCED TRANSFORMATION OF MOUSE 10T1/2 CELLS BY 12-O-TETRADECANOYLPHORBOL-13-ACETATE FOLLOWING EXPOSURE TO X-RAYS OR TO FISSION-SPECTRUM NEUTRONS.

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Cancer Res; 42(2):477-483 1982

Addition of the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) to C3H/10T1/2 cells after exposure to either x-rays or to fission-spectrum neutrons increases significantly the frequency of transformation without any effect on cell survival. However, treatment of unirradiated cells with 0.1 ug of TPA per ml alone results in a small increase in transformation frequency above background (ie, from 1.1 x 10(-5) to 1.0 x 10(-4)). Thus, besides being a promoter, TPA is also a weak initiator. Enhancement of radiation-induced transformation by TPA was relatively greater after low compared to high doses of either radiation. In addition, TPA causes the relative biological effectiveness of neutrons compared to x-rays to increase with increasing dose or with increasing frequency of transformation rather than to decrease, when TPA is not used. For x-ray doses from zero to approx 120 rads, TPA raises transformation to frequencies approx equal to those due to neutrons alone. Analysis of TPA enhancement in the context of the combined effect of two inducing agents, ie, TPA plus a radiation, indicates that with either radiation TPA acts synergistically. Lastly, TPA was found to alter the dependence of transformation frequency on the density of viable cells. As opposed to a constant frequency of transformants per surviving (or viable) cell, which we observed after a fixed dose of x-rays or neutrons for a range of cell inocula the addition of TPA increased the frequency of transformation for all cell inocula (ie, from approx 20 to 6,000 viable cells per 90-mm Petri dish). However, the frequency of transformation decreases with increasing size of the inoculum, a result that we interpret to indicate the combined effect of an interference with cell-to-cell communication by TPA plus the fading of initiation events due to the radiation. (Author abstract) (41 Refs)

39. COORDINATE MUTATION AND TRANSFORMATION OF MOUSE FIBROBLASTS: INDUCTION BY NITROQUINOLINE OXIDE AND MODULATION BY CAFFEINE.

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Carcinogenesis; 2(12):1255-1259 1981

Mutation and malignant transformation were followed in the same cells. Mouse fibroblasts (C3H 10T 1/2) were mutated and transformed by 4-nitroquinoline-1-oxide with similar, approximately linear dose-responses. The presence of caffeine immediately after exposure to 4-nitroquinoline-1-oxide potently inhibited mutation and transformation at high but not at low doses of 4-nitroquinoline-1-oxide. While the coordinate induction of mutation and transformation could be explained by both a common target (DNA) or a common reactive species hitting several targets, the identical modulation by a DNA repair inhibitor of both end points suggests fundamental similarities in the nature of the lesions leading to mutation and transformation and in the processing of these lesions, implying DNA as target and mutation as one (but not necessarily the sole) required step in transformation. (Author abstract) (14 Refs)

40. STARVATION OF ARGININE AND GLUTAMINE SENSITIZES HUMAN DIPLOID CELLS TO THE TRANSFORMING EFFECTS OF N-ACETOXY-2-ACETYL-AMINOFLUORENE.

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Carcinogenesis; 2(12):1303-1310 1981

We have examined the influence of the method of synchronization on the transformation of normal human diploid fibroblasts treated in mid-S phase with N-acetylaminofluorene (N-Ac-AAF), and on the subsequent kinetics of the removal of carcinogen damage. At early times posttreatment, the transformation frequency in cultures synchronized by a 24 hr starvation for arginine and glutamine was enhanced over that of cultures synchronized by release from confluence. In cells synchronized by either method, transformation was enhanced at all times when the cells were incubated after treatment in medium containing high concentrations of nonessential amino acids, vitamins and serum. Synchronized cells treated with 3 uM [3H]N-Ac-AAF in mid-S removed significantly less DNA damage than cultures treated and held under confluent, noncycling conditions. Cells synchronized by amino acid starvation removed less damage than cells synchronized by release from confluence. S-phase treatment of synchronized cells resulted in a dose-dependent delay of DNA replication. The early, rapid phase of repair was temporally correlated with the delay in S-phase progression. We conclude from these data that synchrony achieved by amino acid starvation renders human cells more sensitive to N-Ac-AAF-induced transformation in vitro than does that achieved by release from density-inhibition of growth. The S-phase treated, cycling cells lost only about 10% of their initial carcinogen damage before reinitiation of treatment-delayed bulk DNA synthesis. These results support the hypothesis that the persistence of carcinogen damage in replicating DNA may be an important factor in cell transformation. (Author abstract) (46 Refs)

41. SURFACE REDUCTION OF AMORPHOUS NIS PARTICLES POTENTIATES THEIR PHAGOCYTOSIS AND SUBSEQUENT INDUCTION OF MORPHOLOGICAL TRANSFORMATION IN SYRIAN HAMSTER EMBRYO CELLS.

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Cancer Lett; 15(1):19-26 1982

The proportion of transforming activity of particulate nickel compounds to their phagocyte uptake was studied. Surface reduction of amorphous NiS particles with LiAlH4 increased phagocytosis and the incidence of morphological transformation concomitantly. The incidence of morphological transformation following exposure of Syrian hamster embryo (SHE) cells to crystalline alphaNiS particles was considerably greater than that following a similar exposure to amorphous NiS particles. Increased uptake was observed in solvent-cleaned and surface-reduced crystalline alphaNiS particles. Chemical reduction of the amorph ous NiS particles' surface with LiAlH4 resulted in increase both in their phagocytic uptake by Chinese hamster ovary cells and in their ability to induce transformation in SHE cells. The phagocytosis and transforming activity of crystalline alphaNiS particles was also enhanced by LiAlH4 reduction. The results are consistent with previous observations showing that untreated crystalline NiS particles have a negative surface charge while amorphous NiS particles possess positively charged surfaces. The transforming activity of particulate metal compounds is proportional to their phagocytic uptake. The entry of metal sulfide particles is related to their surface properties and to the degree of negative charge on the surface microenvironment. (27 Refs)

BIOCHEMICAL AND MOLECULAR BIOLOGICAL STUDIES OF TRANSFORMED PHENOTYPE

42. CORRELATION BETWEEN THE LOSS OF THE TRANSFORMED PHENOTYPE AND AN INCREASE IN SUPEROXIDE DISMUTASE ACTIVITY IN A REVERTANT SUBCLONE OF SARCOMA VIRUS-INFECTED MAMMALIAN CELLS.

Fernandez-Pol JA, Hamilton PD, Klos DJ
Nuclear Medicine Lab., Veterans Admin. Medical Center, St. Louis, MO, 63125
Cancer Res; 42(2):609-617 1982

We have studied the effects of paraquat (methyl viologen), a herbicide that increases intracellular production of superoxide radical, on the viability of virus-transformed and nontransformed normal rat kidney (NRK) cells in culture. We have shown that a low concentration of paraquat (12.5 uM) is cytotoxic toward virus-transformed cell lines, including Kirsten sarcoma virus- and SV40-transformed NRK cells. The corresponding untransformed NRK cells were resistant to the same and a four-fold higher concentration of paraquat. There was good correlation between the susceptibility of transformed and untransformed cells to paraquat cytotoxicity and their ability to increase the superoxide dismutase (SOD) enzymatic activity. We found that paraquat is cytotoxic toward Kirsten sarcoma virus-transformed and SV40-transformed NRK cells which showed low intracellular SOD activity. The relationship between SOD activity and paraquat cytotoxicity was strengthened by the finding that the tolerance of NRK cells to the drug was associated with high intracellular SOD activity. This report also describes the isolation of a revertant (revertant RE8G3) cell line derived from Kirsten sarcoma virus-transformed NRK cells after paraquat treatment which contains SOD activity at levels much higher than those found in NRK cells. This revertant is undistinguishable from NRK cells with respect to its lack of transformed cell properties. Not only are these cells normal morphologically but also they do not grow in soft agar, an in vitro property that closely correlates with in vivo tumorigenicity. Several biological and biochemical properties of RE8G3 cells, including growth characteristics, surface receptors for both transferrin and epidermal growth fac tor (EGF), and the EGF-dependent 32P phosphorylation of specific membrane polypeptides have been studied. The most interesting conclusion that can be drawn from these studies is that there is a correlation between loss of the transformed phenotype and an increase in both EGF receptors and EGF-dependent 32P phosphorylation of a mol wt 170,000 membrane-associated protein. (Author abstract) (31 Refs)

43. EXPRESSION OF THE TUMOR ALDEHYDE DEHYDROGENASE PHENOTYPE DURING 2-ACETYLAMINOFLUORENE-INDUCED RAT HEPATOCARCINOGENESIS.

Lindahl R, Evces S, Sheng WL
Biochemistry Program, Univ. Alabama, University, AL, 35486
Cancer Res; 42(2):577-582 1982

In aromatic amine-induced rat hepatomas, the aldehyde dehydrogenase (AIDH) phenotype is qualitatively and quantitatively different from that of normal liver. To identify the mechanism(s) underlying the expression of the tumor-specific AIDHs, we have followed the time course of appearance of the new phenotype during hepatoma formation in Sprague-Dawley rats following brief dietary exposures to 2-acetylaminofluorene (0.02%; 32 days). Tumor promotion by phenobarbital (0.05% in the diet) was also used to compare the effects of a variety of tumor induction protocols on the AIDH phenotype. No change in the AIDH phenotype is detectable by total activity assay, gel electrophoresis, isoelectric focusing, or immunochemical methods during or following exposure to carcinogen or promoter until tumors are grossly observed in liver. Concomitant with tumor appearance, the tumor-specific AIDH phenotype appears. The phenotypic change is limited to the tumor; morphologically and histologically normal liver directly adjacent to the tumor and normal lobes of a tumor-bearing liver do not possess the tumor AIDH phenotype. No correlation exists between tumor size and the degree of deviation of the AIDH phenotype from normal. Nor is there any correlation between the degree of AIDH phenotype deviation and the histology of the various tumors observed. We conclude that the tumor-specific AIDH phenotype is not associated with altered liver metabolism due directly to carcinogen or promoter exposure. Rather, the mechanism of this phenotypic change requires that transformation-associated, stable genetic changes occur in the cells affected by carcinogen that are later expressed as the altered AIDH phenotype. (Author abstract) (22 Refs)

44. ALKALI PHOSPHATASE (ALP) ACTIVITY IN CHICK EMBRYO FIBROBLAST CELLS (CEF) (MEETING ABSTRACT).

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Proceedings of the Japanese Cancer Association 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

It is well known that AlP activity is higher in normal cells than in transformed cells. So we studied the AlP activity in subcultures of CEF and chick cells transformed by a temperature sensitive mutant strain of Rous sarcoma virus (Ta virus). We found the AlP activity at pH 10 is gradually decreased with subculture in a case of CEF which might not be passaged at all finally. In the case of chick cells infected by Ta virus (Ta cells), the AlP activity might be constant. The Ta cells at 40.5 C and CEF look alike in morphological respect even after subculture for a long period (more than a half yr), but the AlP activity is higher than in secondary cells of CEF. The Ta cells at 37 C show transformation under microscope and the AlP activity is lower, but still higher than that of 16th subcultured cells of CEF. These results show the AlP activity is related to a cellular growth condition and also retained by Rous sarcoma virus. A relationship between AlP activity and tumor virus remains to be elucidated. (no Refs)

45. CO-POLYMERIC GLYCOSAMINOGLYCANS IN TRANSFORMED CELLS: TRANSFORMATION-DEPENDENT CHANGES IN THE CO-POLYMERIC STRUCTURE OF HEPARAN SULPHATE.

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Biochem J; 201(1):233-240 1982

Heparin sulfates from normal 3T3 fibroblasts are association-prone as indicated by their affinity for agarose gels substituted with cognate heparin sulfate species. Heparin sulfates from SV40-transformed or polyoma-virus-transformed cells have no affinity for the same gels. Heparin sulfates from the medium, the pericellular and intracellular pools of normal, SV40-transformed and polyoma-transformed 3T3 cells were separated into four subfractions (HS1-HS4) by ion-exchange chromatography. In general, HS1-HS3 were found in cell-derived heparin sulfates, whereas HS3-HS4 were present in the medium. The heparin sulfates from transformed cells were more heterogeneous and of lower charge density than those from the normal counterpart. Degradations via periodate oxidation/alkaline elimination yielded the oligomers glucosamine-(hexuronate-glucosamine)n-R with n = 1-5 and a large proportion of N-sulfate groups. There was a large contribution of fragments n = 4-5 from heparin sulfates of normal cells. These fragments were less common in low-sulfated heparin sulfates of transformed cells. In the case of medium-drived heparin sulfates all species had a low content of fragments n = 4-5. The size distribution of (glucuronate-N-acetylglucosamine)n regions was assessed after deaminative cleavage. It was broad and ranged from n = 1-10 for all heparin sulfate species. In the case of medium-derived heparin sulfates there were distinct differences between normal and transformed cells. In the latter chains the N-acetyl-rich segments were both shorter and longer than in the normal case. The shape of the disaccharide peak was consistent with a lower content of O-sulfate in the heparin sulfates from transformed cells. It was concluded that heparin sulfates from medium or transformed cells exhibit the greatest structural deviation from the normal case. The finding of lower proportions of extended, iduronate/glucuronate-bearing, N-sulfate-rich segments in heparin sulfates of transformed cells was particularly interesting in view of the fact that these elements have been associated with ability to self-interact. (Author abstract) (14 Refs)

46. EUCHROMATIN PROTEIN PHOSPHORYLATION AND NEOPLASTIC TRANSFORMATION (MEETING ABSTRACT).

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Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

Non histone chromosomal proteins (NHCP) are thought to have a specific gene regulatory function. Indentification and characterization of phosphorylated NHCP may provide useful cellular markers for the early onset of neoplasia and may elucidate mechanisms of neoplasia. The experiment design involves an analysis of euchromatin protein alteration during the initial and promotional stages of chemical carcinogenesis as outlined in the Solt-Farber regime. Diethylnitrosamine (DEN) is used as the initiating agent and promoting is achieved through the dietary administration of 2-acetylaminofluorene accompanied by a non-specific growth stimulus-partial hepatectomy. The DNAse I prepared soluble transcriptionally active (euchromatin) fraction is extracted from purified nuclei, labelled with [32P] orthophosphate in primary cell suspension culture. The chromatin proteins are analyzed by two dimensional polyacrylamide gel electrophoresis and autoradiography. Preliminary observations indicate that following a single dose of DEN (200 mg/kg ip), there is acute histological damage to nuclei at one wk and complete recovery within three wk. Electron micrographs of purified nuclei confirmed these findings. Furthermore, electrophoretic analysis of control and DEN treated animals using Coomassie blue visualization of proteins, resulted in the detection of several proteins, not evident in the control animals. (no Refs)

47. ARACHIDONIC ACID TRANSFORMATION AND TUMOR PRODUCTION.

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Adv Cancer Res; 35:49-79 1981

The relationship between arachidonic acid (AA) and cancer is reviewed. Biochemical pathways of AA leading to endoperoxides and several substrates of the lipoxygenases are presented, and prostaglandin (PG) levels in tumors are discussed. AA transformation in relation to hypercalcemia and tumor production is reviewed. Discussion includes the effects of 12-O-tetradecanoyl phorbol-13-acetate (TPA) on PG production of cells in vitro and in vivo and the effect of inhibitors of PG production on TPA activity in cultured cells. Stimulation of PG production by growth factors, the effects of PG on cell or tumor growth, and the relationship between PG and immune response are reviewed. Acylhydrolase activity, or possibly cylooxygenase activity, is more likely than lipoxygenase activity to be causally related to cancer. Future studies concentrating on the mechanism of inhibition of acylhydrolase activity may be important for control of tumor growth. (209 Refs)

CELL SURFACE PHENOMENA OF TRANSFORMATION

48. PURIFICATION AND CELL-SPREADING EFFECT OF GLYCOPROTEIN OF SPONTANEOUSLY MALIGNANT FIBROBLASTS.

Adachi T, Midorikawa O
Dept. Pathology, Faculty Medicine, Kyoto Univ., Kyoto, Japan
Cell Mol Biol; 27(5):445-453 1981

Mouse fibroblast cells (m cells) and so-called reticulum cells (MR cells and SP cells), transformed into malignant cells in vitro, were transferred to a serum-free culture medium, and the morphological and functional differences of these two kinds of cells were studied. We found that the fibroblast cells produce a unique glycoprotein which has the biological function of inducing cell-spreading of so-called reticulum cells on the substratum in the serum-free culture medium. This glycoprotein was purified from the conditioned medium of the transformed fibroblast cells. The mol wt of this protein is about 230-250 x 10(3). The so-called reticulum cells themselves do not produce detectable amounts of this protein. Specific antiserum against this glycoprotein shows a single precipitation line against not only this glycoprotein, but also against serum protein. This antiserum inhibits the cell-spreading-inducing activity of this glycoprotein in vitro. Immunofluorescent microscopy shows that this glycoprotein exists on the cell surface and in the cytoplasm of normal and some transformed fibroblast cells. Undifferentiated fibrosarcoma cells, however, do not produce this glycoprotein in vitro. (Author abstract) (24 Refs)

49. IA-LIKE AND HLA-A,B ANTIGENS ON TUMOR CELLS IN LONG-TERM CULTURE.

Pellegrino MA, Weaver JF, Nelson-Rees WA, Ferrone S, Pious D, Alexander P, Uhr, Lennox ES, Dutton, Doherty PC, Martin WJ, Pollack MS
Dept. Pathology, Coll. Physicians and Surgeons, Columbin Univ., 630 West 168th St., New York, NY, 10032
Transplant Proc; 13(4):1935-1938 1981

Results of screening human tumor cells of nonlymphoid origin for expression of immune region-associated (Ia)-like antigens and human WBC antigen (HLA)-A,B allospecificities are summarized. Fifteen of the 29 tumor cell lines tested adsorbed the anti-Ia-like antigen MoAb Q5/13. Among the cell lines unable to adsorb MoAb Q5/13 were three Simian virus 40-transformed fibroblast lines. Testing of 48 cell lines for the ability to adsorb alloantisera to HLA-A1,A2, A3,A9,A10,B5,B7,B8,B12,B17 detected greater than 2 specificities at the A locus (A1,A2,A3) in the fetal lung line HsiLu and at the B locus (B5,B12, and B17) in the melanoma cell lines Hs 597T and Hs 695T and in the pagetoid sarcoma cell line Hs 925T. In every case, the extraspecificity could be explained by cross-reactivity in the HLA system. One breast carcinoma (Hs 578T) and one melanoma (Hs 695T) cell line tested at several passage levels displayed changes in adsorbing capacity for HLA-A,B alloantisera. Reactivity of cultured human tumor cells with HLA-A,B alloantisera was compared to that of autologous fibroblasts. Results indicate the following: expression of Ia-like antigens on tumor cells of nonlymphoid origin is not restricted to melanomas but may occur on other types of tumors, the HLA-A,B phenotype of tumor cells may change at different passage levels and may differ from that of autologous normal cells, but the changes mainly affect cross-reactivity patterns, and HLA typing may provide useful information to identify cross-species and intraspecies cell line contamination. (5 Refs)

50. DIFFERENT H-2 ANTIGENS EXPRESSED ON TWO TUMORS DERIVED FROM ONE BALB/C MOUSE.

Garrido F, Perez M, Ivanyi P, Schirrmacher V, Alexander P, Martin WJ, Parmiani G, Rogers MJ

Tumor Immunology Unit, C. S. Virgen de las Nieves, Granada, Spain

Transplant Proc; 13(4):1824-1827 1981

Results obtained with the ascitic forms of two solid tumors (B7.2 and B7.3) that arose independently within the same BALB/c mouse are presented. Three independent solid tumors (B7.1, B7.2, and B7.3) had been obtained by inoculation of 0.2 mg methylcholanthrene in different sites of a BALB/c mouse. Solid tumor samples were transformed into the ascitic form and frozen in small aliquots. These ascitic lines were used to study the expression of H-2 antigens; with no other in vivo or in vitro manipulation of the cells was performed. B7.1 and B7.3 tumors grew faster than B7.2. Similar results were obtained when 5 x 10(5) ascitic cells were inoculated sc into BALB/c mice. Regressor mice were obtained only with B7.2 tumor cells. B7.2 and B7.3 ascitic tumor cells were tested in complement-dependent cytotoxicity assays with a panel of anti-H-2 sera of restricted specificity defining private and public H-2 antigens. H-2Dd and H-2Kd private specificities were clearly detected on B7.3 tumor cells. B7.2 tumor cells reacted with antisera directed against the private specificities of H-2k haplotypes and with antisera against the public specificities H-2.1 and H-2.5. Absorption of anti-H-2k alloantisera, private and public specificities, with normal H-2k lymphoid cells removed the anti-B7.2 tumor reactivity. BALB/c anti-B7.2 tumor isoantiserum was tested in a two-stage microcytotoxicity test on normal mouse lymph node cell strains. No reactivity wa s observed with H-2d lymphoid cells (BALB/c and B10.D2); positive reactions were obtained with H-2k, H-2a, H-2r, and H-2q strains. (9 Refs)

51. LACTOPEROXIDASE-CATALYZED IODINATION OF MEMBRANE PROTEINS IN NORMAL AND NEOPLASTIC EPIDERMAL CELLS.

Brysk MM, Snider JM

Dept. Dermatology, Univ. Texas Medical Branch, Galveston, TX, 77550

J Invest Dermatol; 78(1):24-27 1982

Cell surface proteins of normal human, mouse, and rat cells in primary culture, of human basal cell carcinoma, and of carcinogen-transformed cell lines were examined by lactoperoxidase-catalyzed iodination. Autoradiography was used to record the distribution of label in the polypeptide subunits separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis. There was no significant difference in the results for normal cells of human, mouse, and rat. On the other hand, carcinogen-transformed mouse cells had many more labeled polypeptide bands of widely distributed mol wt. The iodination profiles from human basal cell carcinoma cells were much more akin to those from normal cells than to those from carcinogen-transformed cells. Treatment of iodinated cells with proteolytic enzymes visibly altered the polypeptide bands. (Author abstract) (21 Refs)

MORPHOLOGICAL AND OTHER BIOLOGICAL ASPECTS OF ONCOGENIC TRANSFORMATION

52. CYTOSKELETAL AND TRANSMEMBRANE INTERACTIONS IN THE EXPRESSION OF TUMOURIGENICITY IN HUMAN CELL HYBRIDS.

Der CJ, Ash JF, Stanbridge EJ
(c/o Stanbridge) Dept. Microbiology, Coll. Medicine, Univ. California, Irvine, CA, 92717
J Cell Sci; 52:151-166 1981

The cytoplasmic cytoskeletal organization was examined by immunofluorescence analysis in a series of paired non-tumorigenic and tumorigenic HeLa/fibroblast hybrids. The microfilament and microtubule complexity in tumorigenic hybrids was compared to that of the corresponding transformed, non-tumorigenic hybrids from which they were derived. Since both the non-tumorigenic and tumorigenic hybrids displayed well-organized microtubules, the disruption of these cytoskeletal elements is not required for transformation or tumorigenicity. In contrast, the microfilament organization was drastically altered in association with the re-expression of tumorigenicity. However, treatment of these tumorigenic segregant lines with sodium butyrate or dexamethasone resulted in a more flattened morphology and the appearance of well-developed microfilament bundles. This indicated that microfilament complexity was related to cellular morphology and not to tumorigenic potential. Finally, results of double immunofluorescence analyses for microfilaments and fibronectin staining in these hybrids agree with the existence of a transmembrane association between these two systems. In both normal fibroblasts and non-tumorigenic hybrids a close, but not identical, distribution was seen for surface fibronectin and cytoplasmic microfilaments. In the tumorigenic hybrids the lack of a well-organized microfilament system was associated with a much reduced stitched-like pattern for fibronectin. The antibody-induced redistribution of surface beta2-microglobulin reflected this loss of a transmembrane influence on the organization of surface components. Unlike the non-tumorigenic hybrids the tumorigenic segregants possessed an altered extracellular matrix, rounded morphology, and reduced adhesion capabilities. The corresponding reduction in microfilament organization in these hybrids suggests that there is a close interrelationship between these cellular parameters. The exact contribution of these alterations to tumorigenic potential is unclear but the apparent loss of the transmembrane interaction with the cell surface organization may well represent a crucial alteration central to in vivo growth potential. (Author abstract) (48 Refs)

53. CYTOGENETICS OF MURINE THYMIC LYMPHOMAS INDUCED BY N-METHYL-N-NITROSOUREA: DIFFERENCE IN INCIDENCE OF TRISOMY 15 IN THYMIC LYMPHOMAS INDUCED IN NEONATAL AND ADULT MICE.

Chan FP, Ens B, Frei JV
Dept. Anatomy, Health Sciences Center, Univ. Western Ontario, London, Ontario N6A 5C1, Canada
Cancer Genet Cytogenet; 4(4):337-344 1981

Chromosome complements of murine thymic lymphomas induced by an alkylating agent N-methyl-N-nitrosourea (MNUA) were analyzed microscopically and karyotypically using the Q-banding technique. The chemical carcinogen was injected intraperitoneally into either neonatal or 7-wk-old CFW/D mice. In addition, thymic lymphomas induced in 7-wk-old AKR mice and thymic lymphomas developed spontaneously in this strain were also examined. All six lymphomas induced in neonatal CFW/D had hyperdiploid cell lines that accounted for 90% of the cells analyzed. Chromosome analysis of lymphomas induced in adult CFW/D mice showed that only four out of nine lymphomas had predominantly hyperdiploid cell lines. The remaining five lymphomas had diploid modal chromosome number although they also carried a variant line characterized by 41 chromosomes. All eight lymphomas induced in adult AKR mice and six out of seven spontaneous AKR lymphomas showed predominantly diploid modal line. The remaining spontaneous lymphoma had a hyperdiploid stem line of 41 chromosomes. Microscopic and karyotypic analysis further identified trisomy 15 as the regular chromosome abnormality in the hyperdiploid cells in lymphomas of each group, whereas cells with diploid chromosome number had no detectable chromosome abnormality. Additional trisomies were also found, but their appearance was restricted to individual tumors. Thus, the incidence of trisomy 15 in lymphomas induced by MNUA in adult CFW/D and AKR mice, as well as in the spontaneous AKR lymphomas, is significantly lower than t hat in lymphomas induced in neonatal mice by the same carcinogen. (Author abstract) (19 Refs)

54. SPECIFIC CHROMOSOME CHANGES IN VIRUS AND CHEMICAL-TRANSFORMED GLIAL CELLS OF THE RAT (MEETING ABSTRACT).

Kano-Tanaka K, Fukami H, Kato T, Ito J, Tanaka T
Department of Biochemistry, Nagoya City University School of Medicine, Nagoya, Japan
Proceedings of the Japanese Cancer Association 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Karyotypes of 4 malignant cell lines from rat glioblasts transformed by virus (MSV-M-os) and chemical agent were analyzed in early cultures. The modal chromosome number of 3 cell lines was 43 and one was 42. The G-banding pattern revealed that specific change occurred in a No 4 chromosome indicating tandem duplication in all lines. Another change was No 12 trisomy in cells with 43 chromosomes, that was also confirmed using silver staining. The results may suggest the existence of glia-specific and significant genic sites necessary for malignant transformation. (no Refs)

55. ORGANIZATION AND REORGANIZATION OF IMMUNOGLOBULIN GENES IN A-MULV-TRANSFORMED CELLS: REARRANGEMENT OF HEAVY BUT NOT LIGHT CHAIN GENES.

Alt F, Rosenberg N, Lewis S, Thomas E, Baltimore D
Center Cancer Res., Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA, 02139
Cell; 27(2):381-390 1981

The structure of immunoglobulin-related genes was analyzed in individual Abelson murine leukemia virus (A-MuLV)-transformed lymphoid cell lines. Essentially all of these lines, whether immunoglobulin-containing or null, had DNA rearrangements in the vicinity of the JH regions on both chromosomes as well as deletions of at least 5 kb of DNA 5' to JH. None of these lines, however, except rare light chain producers had detectable rearrangements at either their kappa or lambda light chain loci. In contrast to A-MuLV-transformants derived from bone marrow, those from early fetal liver frequently contained more than 2 and sometimes 12 or more distinct, rearranged JH-containing fragments. Cellular subclones derived from these lines had a subset, usually two, of the fragments found in the parent line. Therefore, heavy chain gene rearrangement appears to precede that of light chain gene rearrangement and is still continuing in certain cultured A-MuLV transformants. (Author abstract) (43 Refs)

56. CHARACTERIZATION OF A BONE MARROW CELL LINE TRANSFORMED BY ABELSON'S MURINE LEUKEMIA VIRUS.

Pinter A, Borzsonyi M
Orszagos Kozegeszsegugyi Intezet, Budapest, Hungary
Magy Onkol; 25(4):217-226 1981

Development of transformed cell line (Gr 17) was observed after infection of a long-term bone marrow cell culture from BALB/c mice with Abelson's murine leukemia virus (strain P 160) (A-MuLV). According to their phenotype, the Gr 17 cells corresponded to the early maturation form of B lympho id cells (pre-B lymphoblasts). The results of the tests for alpha-naphthylacetate esterase, Hb, phagocytosis, and membrane surface Ig were negative, but cytoplasmic IgM was found. In contrast to the hitherto described cell lines obtained by transformation with A-MuLV, hypodiploid chromosome set and the presence of metacentric chromosome due to translocation were observed. Development of thymus-independent generalized lymphoma was observed after transplantation of Gr 17 cells (2 x 10(7) cells iv) in 4-6-wk-old male and female BALB/c mice. The take rates were 9/10 in the females and 8/10 in the males. The mean latent periods were 41 days in the females and 50 days in the males. Typical Abelson's tumors were induced by the virus produced by the cell line in newborn BALB/c mice. (27 Refs) (In HUN)

57. BLOCK IN THE EXPRESSION OF DIFFERENTIATION MARKERS OF RAT THYROID EPITHELIAL CELLS BY TRANSFORMATION WITH KIRSTEN MURINE SARCOMA VIRUS.

Fusco A, Pinto A, Tramontano D, Tajana G, Vecchio G, Tsuchida N
(c/o Vecchio) Instituto di Patologia Generale, Universita de Napoli, Naples 80131, Italy
Cancer Res; 42(2):618-626 1982

Well-differentiated epithelial cells, derived from primary cultures of normal rat thyroid glands (T-79 cells), as well as a cloned cell line also derived from normal rat thyroid glands (FRT-L cells) were infected with Kirsten murine sarcoma virus carrying outer coat of the helper Kirsten murine leukemia virus. Infected T-79 and FRT-L cells changed morphologically and began to proliferate rapidly, suggesting malignant transformation by the virus. Both cell lines can support the replication of both transformation-competent and transformation-incompetent viruses such as murine or rat leukemia viruses. Infected T-79 and FRT-L cells had a high colony-forming efficiency (68 and 64%, respectively) when grown in agar and formed tumors when transplanted sc into syngeneic rats. These tumors morphologically resemble undifferentiated adenocarcinomas, thus showing that Kirsten sarcoma virus carrying the outer coat of the helper Kirsten murine leukemia virus is able to transform differentiated epithelial cells. Transformed T-79 and FRT-L cells, in contrast to uninfected cells, neither secrete thyroglobulin nor concentrate iodide, two biochemical markers of differentiated thyroid function. Thus, expression of the differentiated phenotype is blocked as a consequence of cell transformation. The system described may be useful in studying epithelial cell carcinogenesis in terms of regulated expression of differentiated functions. (Author abstract) (34 Refs)

58. A NUCLEAR ANTIGEN ASSOCIATED WITH CELL PROLIFERATION AND BLAST TRANSFORMATION. ITS DISTRIBUTION IN SYNCHRONIZED CELLS.

Takasaki Y, Deng JS, Tan EM
Div. Rheumatic Diseases, Dept. Medicine, Univ. Colorado Sch. Medicine, Denver, C O, 80262
J Exp Med; 154(6):1899-1909 1981

The time relationship of nuclear antigen present in proliferating cells (PCNA) to synthesis of DNA, RNA, and protein during the cell cycle was examined. Two sera (EB and MN) from patients with systemic lupus erythematosus contained precipitating anti-PCNA antibody along with antibodies to other nuclear antigens. Insolubilized rabbit kidney extract was used as an immunoadsorbant; precipitating antibodies to other nuclear antigens were removed with the exception of anti-PCNA. WiL-2 diploid human B lymphocytes were examined with EB-absorbed serum at different phases of synchronized growth. At G0, immediately after release from density-dependent arrest, PCNA were present as speckled nucleoplasmic staining. At 12 hr, nucleolar staining and speckled nucleoplasmic staining were evident. At 20 hr, nucleolar staining had disappeared from most cells, but speckled nucleoplasmic staining was strong. In mitosis, staining was more intense in areas peripheral to chromosome condensation, but radiating strands of staining could be seen within the region of chromosome condensation. In WiL-2 cells, nucleolar staining predominated in a period which overlapped late G1 and early S, while in phytohemagglutinin-stimulated lymphocytes, nucleolar staining was the dominant pattern well before DNA synthesis occurred. Results demonstrate that the relationship of PCNA to proliferation and blast transformation may be associated with events related to DNA synthesis in the cells. (14 Refs)

59. MOLECULAR MECHANISMS INVOLVED IN MORPHOLOGICAL VARIATION OF AVIAN SARCOMA VIRUS-INFECTED RAT CELLS.

Chiswell DJ, Enrietto PJ, Evans S, Quade K, Wyke JA
(c/o Wyke), Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England
Virology; 116(2):428-440 1982

Clones of avian sarcoma virus (ASV)-infected rat cells are heterogeneous, containing both morphologically transformed and morphologically normal cells. Morphological variation is reversible: normal cells can give rise to transformed daughters and they in turn can segregate morphologically normal revertants. However, reversion of transformed clones seems to occur more readily than transformation of normal cells. In most cases, morphologically normal cells contain recoverable viruses with no defect in transformation and yet the cells themselves are usually fully susceptible to transformation by superinfecting ASV. With one exception, morphological changes are not accompanied by detectable alterations in the size or chromosomal location of the single ASV provirus that these clones possess. In one clone, A11, that has been examined in detail, transformed segregants contain virus specific RNAs and the viral transforming protein, pp60src, whereas in normal subclones neither RNA nor protein can be detected. These results indicate that morphological variation reflects a reversible modulation in expression of viral functions, probably specific to individual proviruses and probably operating at the level of viral RNA transcription. (Author abstract) (33 Refs)

ASSAYS OF ONCOGENIC TRANSFORMATION

60. A NEW PROTOCOL AND ITS RATIONALE FOR THE STUDY OF INITIATION AND PROMOTION OF CARCINOGENESIS IN RAT LIVER.

Potter VR
McArdle Lab. Cancer Res., Univ. Wisconsin Medical Sch., Madison, WI, 53706
Carcinogenesis; 2(12):1375-1379 1981

A new protocol for carcinogenesis in rat liver is described in order that confirmatory experiments might be undertaken concurrently. The basic protocol, designated IPI (initiator plus promoter plus initiator), is presented in several alternative forms including the possible use of x-irradiation as the initiator. The rationale is discussed in terms of the two-hit somatic mutation theory of Armitage and Doll, with an initial hit produced by the first dose of initiator and expansion of single cells to sizable clones by promotion thereby increasing the probability of a second hit by the second dose of initiator. The question of relevant mutations is taken up and it is proposed that genes for chalones and for chalone receptors are logical targets for consideration in a two-mutation sequence. (Author abstract) (33 Refs)

61. A NEW METHOD TO ESTABLISH THE CLONOGENICITY BY TUMORIGENIC DIPLOID CELLS IN THE SOFT AGAROSE CULTURE (MEETING ABSTRACT).

Hatanaka M
Kyoto University, Kyoto, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Transformed and tumorigenic cells are known to form colonies in the soft agar culture indicating the acquisition of anchorage independency. However, cells derived from malignant tumors, fail frequently the clonogenicity under the similar conditions. Our isolates of the tumorigenic Indian muntjac cells which maintained the stable diploidy throughout in vitro transformation and in vivo tumorigenesis, demonstrated no colony formation in the soft agar. A new method of colony formation by these cells has been developed. The co-cultivation of other tumor cells was required to form colonies in the soft agarose. Raji-TK-(a cell line of Burkitt lymphoma deficient of thymidine kinase) cannot replicate under the conditional media (hypoxanthine, amethopterin and thymidine), though the cell can supply a factor(s) to promote the clonogenicity of the tranformed diploid cells. This may provide a promising method of the clonogenicity of human primary tumors that have been unsuccessful in the conventional soft agar culture. (no Refs)

62. CHARACTERIZATION OF SPONTANEOUS AND MNNG-TRANSFORMED CELL LINES DERIVED FROM SYRIAN HAMSTER (MEETING ABSTRACT).

Matsuya Y, Kato M, Yamane I
Tohoku University, Sendai, Japan
Proceedings of the Japanese Cancer Association 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Culture of neonatal Syrian hamster lung developed into established cell lines in epidermal growth factor-supplemented medium. The contact-inhibited lines appeared under the condition of low saturation densities and the chromosome number was in tetraploid range. Diploid lines were also isolated from the culture and produced rarely spontaneous transformants during serial culture. The lines became dominant in the population and the chromosome distribution ranged from hypodiploid to hypertetraploid. The cultured line could be transformed by treatment with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and the transformants formed foci showed piling up. The culture was composed of diploid and tetraploid cells. The tumorigenicity of spontaneous and MNNG-transformed cells is now being tested. (no Refs)

63. ESTABLISHMENT OF B-LYMPHOBLASTOID CELL LINES FROM MAREK'S DISEASE VIRUS-INDUCED TUMORS IN TURKEYS.

Nazerian K, Elmubarak A, Sharma JM
Regional Poultry Res. Lab., U. S. Dept. Agriculture, 3606 East Mount Hope Road, East Lansing, MI, 48823
Int J Cancer; 29(1):63-68 1982

Four lymphoblastoid cell lines were established from tumors of turkeys inoculated with high doses of the GA strain of Marek's disease virus (MDV). Unlike other MD lymphoblastoid cell lines of chicken origin, these MDV transformed turkey lines appear to be B lymphocytes and produce immunoglobulin. Growth characteristics of these cell lines are slightly different; however, they all produce low levels of MDV-specific antigen and carry the complete genome of the virus as determined by virus rescue in the chicken or in duck embryo fibroblast cultures. These cell lines are pathogenic for chickens and produce virus-induced MD lesions. All four lines are free of the herpesvirus of turkeys, reticuloendotheliosis virus, and three lines are also free of avian leukosis virus. They all have typical normal turkey chromosomes and are positive for Marek's disease tumor-associated surface antigen. (Author abstract) (24 Refs)

GENERAL REVIEWS AND OTHER RELATED STUDIES

64. CURRENT CONCEPTS AND CONTROVERSIES IN CHEMICAL CARCINOGENESIS.

Weinstein IB
Div. Environmental Sciences, Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 17(2):99-120 1981

Fundamental research at the cellular and molecular levels on mechanisms of action of chemical carcinogenesis and applied aspects and the concept of 'molecular epidemiology' of cancer are reviewed. The action of initiating agents and their metabolism and covalent binding to macromolecules is discussed under the following headings: metabolic activation, carcinogen potency, structures of carcinogen-DNA adducts, conformational changes in DNA, carcinogen modification of mitochondrial DNA, DNA repair, and carcinogen-DNA modification and mechanism of initiation. Tumor promotion and multifactor interactions are discussed in relation to two-stage skin carcinogenesis. Numerous effects elicited by phorbol ester tumor promotors, particularly 12-O-tetradecanoyl-phorbol-13-acetate, are classified into three categories: mimicry of transformation, modulation of differentiation, and membrane effects. Also considered in relation to phorbol ester tumor promotors, tumor promotion, and multifactor interactions are phorboid receptors, ion flux, possible role of kinases, chromosomal effects and activated oxygen, and chemical-viral interactions. The tumor-promoting activity of polycyclic aromatic hydrocarbons is discussed. A unified theory of tumor initiation and promotion is presented. Molecular epidemiology and cancer prevention are discussed with regard to limitations of current approaches and molecular cancer epidemiology. (94 Refs)

65. POLYOMA T ANTIGENS.

Eckhart W
Tumor Virology Lab., Salk Inst., San Diego, CA, 92138
Adv Cancer Res; 35:1-25 1981

Current knowledge on polyoma T proteins is reviewed, including the role of these viral-coded proteins in lytic infection of mouse cells, DNA nucleotide sequences (coding and regulatory signals), mutations affecting the T antigens, and cell transformation and tumorigenicity. The T antigens are compared structurally with SV40 in terms of nucleotide sequences. The roles of the large, small, and medium T antigens in lytic infection and transformation are discussed. The functions associated with small and medium T antigens, particularly attempts to detect protein kinase activity associated with polyoma T, are reviewed. (110 Refs)

66. TRANSFORMATION INDUCED BY HERPES SIMPLEX VIRUS: A POTENTIALLY NOVEL TYPE OF VIRUS-CELL INTERACTION.

Hampar B
Lab. Molecular Virology, NCI, Frederick, MD, 21701
Adv Cancer Res; 35:27-47 1981

Three areas of the literature on herpes simplex virus (HSV) transformation induction are reviewed: HSV-induced transformation in vitro, the contrast between HSV in vitro transformation studies and transformation induced by other DNA viruses, and mechanisms of transformation in the HSV system. Models for in vitro transformation by HSV include use of nonpermissive cells, use of virus-host range mutants, use of inactivated viruses, use of temperature-sensitive virus mutants, and use of virus DNA or restriction enzyme-digested DNA fragments. Properties of biochemically transformed cells, morphologically, and tumorigenically transformed cells, and persistence of HSV genetic material in these cells, are discussed. The major problem remaining in elucidating the role of HSV in transformation is the lack of a system in which significant levels of transformation can be obtained reproducibly. (96 Refs)

67. THE SHOPE PAPILLOMA-CARCINOMA COMPLEX OF RABBITS: A MODEL SYSTEM OF NEOPLASTIC PROGRESSION AND SPONTANEOUS REGRESSION.

Kreider JW, Bartlett GL
Dept. Pathology, Milton S. Hershey Medical Center, Hershey, PA, 17033
Adv Cancer Res; 35:81-110 1981

Shope papilloma virus (SPV), an indigenous disease in rabbits of the high plains of the United States that is transmissible to other rabbits, is discussed as a model of neoplastic progression and spontaneous regression. Topics include historical origins of the model, the interaction of SPV and host cells (natural occurrence and transmission, virion and genome structure, factors influencing SPV replication, the rabbit kidney vacuolating virus, host cell specificity, cell and tissue culture studies, papilloma arginase), neoplastic progression (malignant transformation, factors influencing neoplastic progression, the role of SPV genome in carcinomatous transformation), and spontaneous regression (growth, genetic and immunological factors in spontaneous regression). Theoretical and practical aspects of the Shope papilloma-carcinoma complex as a model system are advanced; the relevance to human neoplasia is considered. (123 Refs)

68. REGULATION OF SV40 GENE EXPRESSION.

Graessmann A, Graessmann M, Mueller C
Institut fur Molekularbiologie und Biochemie, Freien Universitat Berlin, Berlin, W. Germany
Adv Cancer Res; 35:111-149 1981

The microinjection approach to the study of simian virus 40 (SV40) and polyoma virus (PV) gene expression is discussed. The technique permits placing of biological material from virtually any source directly into living, single-tissue culture cells using glass micropipettes. Cell type dependence of SV40 and PV gene expression is presented in relation to permissive, nonpermissive, semi-permissive, and virus-resistant cells. Functions of SV40 tumor antigens are considered, including induction of cellular and viral DNA systems, regulation of late and early SV40 gene expression, stimulation of rRNA synthesis, helper function for adenovirus and U antigenicity, and reduction of the actin cable structure. Experiments with microinjection of SV40 DNA fragments to induce cellular transformation and applications of microinjection are reviewed. (78 Refs)

69. POLYAMINES IN MAMMALIAN TUMORS PART 1.

Scalabrino G, Ferioli ME
Inst. General Pathology, Univ. Milan, 20133 Milan, Italy
Adv Cancer Res; 35:151-268 1981

The connection between polyamines (PA) and cancer in mammals is reviewed, and evidence of a relationship between PA and neoplastic disease is evaluated. Biochemical and metabolic aspects discussed include properties of the PA biosynthetic enzymes S-adenosyl-L-methionine, 5'-methylthioadenosine, catabolism of major PA in mammals, conjugation and excretion products, and natural antibodies of PA. Levels of PA and biosynthetic enzymes in experimental tumors and modifications of in vivo and in vitro metabolism of PA by chemical carcinogens and tumor promoters (single and repeated promoter administration, multistage carcinogenesis, mutagenic and antimutagenic properties of PA) are reviewed. PA levels in urine, serum, and erythrocytes of rats during chemical carcinogenesis or when bearing several experimental tumors are considered. Effects of oncogenic RNA and DNA viruses in biosynthesis, levels of PA in cells during virus-induced transformation, and the role of physical carcinogens in changes in PA biosynthesis and content of target tissues are reviewed. (894 Refs)

70. ONCOGENESIS BY RNA TUMOR VIRUSES.

Koyama T
Dept. Carcinostasis Res., Tokyo Univ. Medical Res. Inst., 4-6-1 Kindai, Minato-ku, Tokyo 108, Japan
Tanpakushitsu Kakusan Koso; 26(14):2121-2129 1981

The origin of retrovirus transforming genes and their oncogenic mechanisms were discussed with respect to literature data. Existence of oncogenic genes in lymphogenous leukemia virus, sarcoma viruses, and acute leukemia viruses was discussed. Oncogenic mechanisms of sarcoma viruses, acute leukemia viruses, and lymphogenous leukemia viruses were reviewed with the aid of analysis at the nucleic acid or protein levels. Various research showed that oncogenesis by retroviruses was not only due to promoter insertion; changes in the manifestation of the c-oncogenic gene, by introduction of DNA rearrangement methods, were also thought to be possible. (77 Refs) (In JPN)

71. ONCOGENES. A UNITARY CAUSE OF CANCER?

Erikson RL
4200 E Ninth Ave., Denver, CO, 80262
JAMA; 247(2):178-181 1982

The sarc gene and the sarc gene product of Rous sarcoma virus, relevance of tumor viruses to human cancer, number of transforming genes in RNA viruses, and usefulness of retroviruses in cancer research are discussed. The sarc gene induces fibrosarcomas in susceptible animals and causes malignant transformation of cultured fibroblasts. Its product is a 60,000-dalton phosphoprotein that is concentrated in plasma membranes of transformed cells; the protein has protein kinase activity and phosphorylates tyrosine residues in immunoglobulins and cellular proteins. Through genetic recombination, RNA tumor viruses have acquired host-cell genes in addition to the sarc gene. Following viral reinfection, the cellular genes are capable of transforming a second host cell into a cancer cell. Although sarc and cellular genes initiate the transformation process through overproduction of gene products, a gene-specific substrate may be necessary to achieve transformation. A schematic diagram shows the malignant transformation of a normal cell after infection with avian sarcoma virus. (no Refs)

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As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. ETHYLENE OXIDE (ETO): EVIDENCE OF CARCINOGENICITY.
Coene RF
National Inst. for Occupational Safety and Health, Cincinnati, OH
Vet Hum Toxicol; 23(6):439-443 1981

DIETARY FACTORS IN CARCINOGENESIS

2. NUTRITIONAL ASPECTS OF CANCER PREVENTION: AN OVERVIEW.
Silverman J
American Health Foundation, Naylor Dana Inst Disease Prevention, Valhalla, NY, 10595
J Am Vet Med Assoc; 179(12):1404-1409 1981

3. FORMATION OF N-NITROSO COMPOUNDS IN FOODS.
Gray JI
Dept. Food Science and Human Nutrition, Michigan State Univ., East Lansing, MI, 48824
ACS Symp Ser; 174():165-180 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

4. LYMPHOMAS AND LEUKAEMIAS. PART 2: TROPICAL AMERICA.
Jimenez E
Hospital Nacional de Ninos 'Dr. Carlos Saenz Herrera', Apartado 1654, San Jose, Costa Rica
Clin Haematol; 10(3):894-915 1981

5. LYMPHOMAS AND LEUKAEMIAS. PART 1: TROPICAL AFRICA.
Olweny CL
Uganda Cancer Inst., P.O. Box 3935, Kampala, Uganda
Clin Haematol; 10(3):873-893 1981

6. MALIGNANT MELANOMA.
Creagan ET
Div. Medical Oncology, Mayo Clinic, Rochester, MN, 55905
Compr Ther; 7(12):36-44 1981

7. MELANOTIC TUMORS OF THE UVEA AND RETINA.
Schmitt H
Universitats-Augenklinik, Theodor-Stern-Kai 7, D-6000 Frankfurt am Main, W. Germany
Med Klin; 76(24):672-675 1981
In GER

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

8. THE NATURAL HISTORY OF CARCINOGENESIS: IMPLICATIONS OF EXPERIMENTAL CARCINOGENESIS IN THE GENESIS OF HUMAN CANCER.
Pitot HC, Goldsworthy T, Moran S
McArdle Lab. for Cancer Res., Dept. Oncology, Medical Sch., Univ. Wisconsin, Madison, WI, 53706
J Supramol Struct Cell Biochem; 17(2):133-146 1981

9. CURRENT CONCEPTS AND CONTROVERSIES IN CHEMICAL CARCINOGENESIS.
Weinstein IB
Div. Environmental Sciences, Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 17(2):99-120 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

10. BURKITT'S LYMPHOMA.
Ambrus JL, Ambrus CM
Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Med; 12(6):385-413 1981

11. PRIMARY HEPATIC CARCINOMA.
Iosquin CJ
Catedra de Medicina Interna A, Facultad de Ciencias Medicas, La Plata, Argentina
Rev Fac Cienc Med La Plata; 4(2):27-31 1981
In SPA

METHODOLOGY IN CARCINOGENESIS RESEARCH

12. MUTAGENESIS AND CARCINOGENESIS TESTING IN VITRO.
Casto BC
Northrop Services, Incorporated, P.O. Box 12313, Research Triangle Park, NC, 27709
Biotechnol Bioeng; 23(12):2659-2671 1981

OTHER REVIEWS IN CARCINOGENESIS

13. CANCER IN THE YEAR 2000. A REVIEW.
Saxen E
Suomen Syoparekisteri, Liisankatu 21 B, 00170 Helsinki 17, Finland
Duodecim; 97(20):1708-1716 1981
In FIN

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SERIES CK14 No. 82/07

JULY, 1982

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TRANSFORMATION GENE STRUCTURE

1. FUNCTION OF THE RETROVIRUS LONG TERMINAL REPEAT.

Temin HM
McArdle Lab., Univ. Wisconsin, Madison, WI, 53706
Cell; 28(1):3-5 1982

The long terminal repeat (LTR), a series of nucleotides derived from the 5' and 3' ends of viral RNA and located at the end of all infectious retrovirus DNA, is described. Information obtained from studies of the morphological transformation of NIH/3T3 cells after treatment with DNA containing LTR sequences and cellular homologs of viral transforming genes (oncogenes) is presented. Other data about LTR has been obtained from recombination of LTR from mouse mammary tumor virus with coding sequences. The presence of LTR has been used to explain differences in leukemogenicity of recombinant avian leukosis viruses. Evidence for the role of the ends of the LTR in processes related to integration is described. The LTR appears to contain most of the sequences involved in making retroviruses autonomous replicating elements. The relationship among viral, cellular, and LTR DNA is considered. (no Refs)

2. STRUCTURAL RELATIONSHIP BETWEEN A NORMAL CHICKEN DNA LOCUS AND THE TRANSFORMING GENE OF THE AVIAN ACUTE LEUKEMIA VIRUS MC29.

Robins T, Bister K, Garon C, Papas T, Duesberg P
Dept. Molecular Biology, Univ. California, Berkeley, CA, 94720
J Virol; 41(2):635-642 1982

We screened a recombinant chicken DNA/lambda phage library for sequences homologous to the transformation-specific sequences of the avian acute leukemia virus MC29 by hybridization with molecularly cloned MC29 proviral DNA. Three cellular DNA clones were found and compared with each other and with the viral genome by physical mapping with restriction endonucleases and by heteroduplex analysis. These experiments indicated that the three cellular clones overlap and represent a single cellular locus. The RNA genome of MC29 and normal cell DNA share a homologous region of 1.6 kilobases which is interrupted in the cellular DNA by 1.0 kilobase of sequences not present in the viral genome. Hybridization of the cloned cellular DNA to viral RNA and analysis of the protected viral RNA by fingerprinting techniques indicated that there is extensive sequence homology between the helper virus-unrelated mcv sequences of the viral RNA and the cellular DNA, with only minor base differences. The cellular mcv locus, however, lacks all helper virus-related sequences of MC29, including those of the partial viral gag gene which, together with mcv, encodes the probable transforming protein of MC29. We conclude that although the mcv locus of the normal cell does not represent a complete structural homolog to the onc gene of MC29, it is probably the precursor to the onc-specific sequence in the virus. (Author abstract) (27 Refs)

3. ISOLATION AND CHARACTERIZATION OF CHICKEN DNA HOMOLOGOUS TO THE TWO PUTATIVE ONCOGENES OF AVIAN ERYTHROBLASTOSIS VIRUS.

Vennstrom B, Bishop JM
Dept. Microbiology, Univ. Uppsala, Biomedical Center, Uppsala, Sweden
Cell; 28(1):135-143 1982

The genome of avian erythroblastosis virus contains two independently expressed genetic loci (v-erbA and v-erbB) whose activities are probably responsible for oncogenesis by the virus. Both loci are closely related to nucleotide sequences found in the DNA and RNA of chickens and other vertebrates. We have isolated and characterized chicken DNA homologous to v-erbA and v-erbB. The two viral genes are represented by separate domains within chicken DNA (c-erbA and c-erbB), which are separated by a minimum of 12 kilobases (kb) of DNA and may not be linked at all. The nucleotide sequences shared by the viral and cellular erb loci are colinear, but the cellular loci are interrupted by multiple intervening sequences of various lengths. Polyribosomes prepared from normal chicken embryos contain two polyadenylated RNAs transcribed from c-erbA and two transcribed from c-erbB. The evident coding regions of these RNAs represent an unusually small fraction of the lengths of the RNAs, as if the 3' untranslated domains of the RNAs might be exceptionally large (3-11 kb). These findings indicate that the c-erb loci are normal vertebrate genes rather than genes of cryptic endogenous retroviruses, and that they may have a role in the metabolism of normal cells. It appears that the viral erb genes, like most other retrovirus oncogenes, have been copied from cellular genes. In the viral genome, the two genes are devoid of introns, but they remain independently expressed loci, and they remain colinear with the coding domains of their cellular progenitors. (Author abstract) (30 Refs)

4. GENOME STRUCTURE OF THE DEFECTIVE AVIAN SARCOMA VIRUS PRCIV.

Wong TC, Hirano A, Lai MM, Vogt PK
(c/o Vogt) Dept. Microbiology, Univ. Southern California Sch. Medicine, 2011 Zonal Ave., Los Angeles, CA, 90033
Virology; 117(1):156-164 1982

The genome of PRCIV, a defective avian sarcoma virus of class II, was studied by nucleic acid hybridization and oligonucleotide mapping. It has a length of about 6.1 kilobases (kb). A stretch of retrovirus replicative sequences encompassing part of the gag, all of the pol, and most of the env region, in all about 5 kb, is deleted. In its place a 2.9 kb substitution that is transformation-specific for PRCIV was found. Flanking the PRCIV-specific substitution are sequences shared with the helper virus, a stretch of 2.0 kb on the 5'-side, including part of the gag region, and a stretch of up to 1 kb on the 3'-side, including the C-region and possibly some env sequences. A PRCIV-specific cDNA probe representing the transformation-specific sequences was prepared. This probe hybridizes only with RNAs of other class II sarcoma viruses but fails to hybridize with either class I or class III sarcoma viruses. (Author abstract) (25 Refs)

5. ISOLATION OF A TRANSFORMATION-DEFECTIVE DELETION MUTANT OF MOLONEY MURINE SARCOMA VIRUS.

Evans LH, Duesberg PH
(c/o Duesberg) Dept. Molecular Biology, Univ. California, Berkeley, CA, 94720
J Virol; 41(2):735-743 1982

A transformation-defective (td) deletion mutant of Moloney murine sarcoma virus (td Mo-MSV) and a transforming component termed Mo-MSV 3 were cloned from a stock of clone 3 Mo-MSV. To define the defect of the transforming function, the RNA of td Mo-MSV was compared with those of Mo-MSV 3 and of another transforming variant termed Mo-MSV 124 and with helper Moloney murine leukemia virus (Mo-MuLV). The interrelationships among the viral RNAs were studied by fingerprinting and mapping of RNase T1-resistant oligonucleotides (T1-oligonucleotides) and by identification of T1-oligonucleotides present in hybrids formed by a given viral RNA with cDNA's made from another virus. A comparison of td Mo-MSV sequences with either Mo-MSV 124 or Mo-MSV 3 indicated directly, in a fashion similar to the deletion analyses which defined the src gene of avian sarcoma viruses, that Mo-MuLV-unrelated sequences of Mo-MSV are necessary for transformation. A definition of transformation-specific sequences of Mo-MSV by deletion analysis confirmed and extended previous analyses which have identified Mo-MuLV-unrelated sequences in Mo-MSV RNA and other studies which have described transformation of mouse 3T3 fibroblasts upon transfection with DNAs containing the Mo-MSV-specific sequence. (29 Refs)

6. MOLONEY MURINE LEUKEMIA VIRUS-INDUCED TUMORS: RECOMBINANT PROVIRUSES IN ACTIVE CHROMATIN REGIONS.

van der Putten H, Quint W, Verma IM, Berns A
Departement de Biologie Animale, Laboratoire de Differenciation Cellulaire, 154, Route de Malagnou, CH-1224, Chene-Bougeries, Geneve, Switzerland
Nucleic Acids Res; 10(2):577-592 1982

The DNase I sensitivity of chromosomal DNA regions carrying integrated proviral genomes of Moloney (M-MuLV) and AKR Murine Leukemia Virus (AKR-MuLV), and the cellular homologue of the mos-gene (c-mos) of Moloney Sarcoma Virus (MSV) were studied in tumor tissues of leukemic mice. The genetically transmitted sequences of M-MuLV, AKR-MuLV, and the c-mos gene are all in DNase I resistant chromatin conformations in M-MuLV-induced tumors. Each M-MuLV-induced tumor contained at least one somatically acquired integrated recombinant MuLV genome that displayed two main characteristic features of active chromatin; (a) a configuration hypersensitive to DNase I, and (b) extensive hypomethylation. DNase I hypersensitive sites were mapped at the junction of cellular sequences and the 5'-viral large terminal repeat (LTR). Expression of a recombinant MuLV seems therefore to be a necessary feature to maintain the transformed state. (Author abstract) (28 Refs)

7. PRIMATE ORIGIN OF THE CELL-DERIVED SEQUENCES OF SIMIAN SARCOMA VIRUS.

Robbins KC, Hill RL, Aaronson SA
Lab. Cellular and Molecular Biology, Natl. Cancer Inst., Bethesda, MD, 20205
J Virol; 41(2):721-725 1982

We sought to identify the species of origin of the cell-derived (sis) sequences of simian sarcoma virus. A molecular clone comprised of sis DNA detected related nucleotide sequences at low copy numbers in normal cellular DNAs of species as diverse as humans and quail. The extent of hybridization and degree of base-pair matching with sis DNA were greatest with New World primate DNAs. The thermal denaturation curve midpoints of hybrids formed between sis and woolly monkey DNAs were indistinguishable from homologous sis DNA hybrids, establishing the woolly monkey (Lagothrix spp) as the source of sis sequences. In comparative studies, sis was shown to be more conserved among mammalian species than unique-sequence woolly monkey cellular DNA. There was no detectable homology between cis and the cell-derived sequences of other fibroblast-transforming retroviruses. These findings indicate that sis is likely to be a unique onc gene among transforming retroviruses. (Author abstract) (35 Refs)

8. PROTEINS CONTAINING ONLY HALF OF THE CODING INFORMATION OF EARLY REGION 1B OF ADENOVIRUS ARE FUNCTIONAL IN HUMAN CELLS TRANSFORMED WITH THE HERPES SIMPLEX VIRUS TYPE 1 THYMIDINE KINASE GENE AND ADENOVIRUS TYPE 2 DNA.

Klessig DF, Quinlan MP, Grodzicker T
Dept. Cellular, Viral and Molecular Biology, Univ. Utah, Salt Lake City, UT, 84132
J Virol; 41(2):423-434 1982

We introduced into tk- human 143 cells adenovirus Type 2 (Ad2) genes by transformation with a plasmid (p711) containing both Ad2 sequences and the herpes simplex virus Type 1 (HSV-1) tk gene. p711 contained approximately the left 8% of the Ad2 genome inserted in the HindIII site of pBR322, whereas the fragment of HSV-1 containing the tk gene was inserted in the BamHI site. Three tk+ cell lines were isolated after selection in HAT medium. The arrangement of viral sequences in the three transformants was analyzed by restriction endonuclease digestion and filter hybridization. All three lines contained a single insertion of Ad2 DNA which was present at approximately one copy per cell. The arrangement of Ad2 sequences in these lines was identical to that found in the linear p711 DNA used in the transformation. S1 analysis of the Ad2-specified RNA from two of these lines indicated that the early region 1a mRNA's were synthesized, though in lower amounts than found in lytic infections. These cell lines contained only the left half of early region 1b (4.6 to 11.2), which encoded the 5' portion of the 1b mRNA's. A complex pattern of 1b RNAs was made in these cell lines. Transcription of most of these RNAs began at or near the 1b promoter and proceeded through the 1b sequences into the flanking pBR322, HSV-1, or host sequences. Since many of the RNAs were terminated or spliced in the HSV-1 (anti-sense strand) or pBR322 sequences, new RNA processing sites must be used in the formation of these mRNA's. All three lines fully complemented the 1a deletion mutant Ad5 dl312. Surprisingly, these lines also permitted the growth of 1b deletion mutants (Ad5 dl313 and Ad5 dl434), although the complementation was not always complete. Presumably the new gene product(s) which contained only part of the 1b gene provided most of the essential function(s) required for viral multiplication. Alternatively, the 1b 19-kilodalton protein which was entirely encoded by the adenovirus sequences present in these cell lines was sufficient for viral growth even in the absence of the 1b 55-kilodalton protein. (Author abstract) (50 Refs)

TRANSFORMATION GENE EXPRESSION AND REGULATION

9. CHANGES IN GENE EXPRESSION ACCOMPANYING CHEMICALLY-INDUCED MALIGNANT TRANSFORMATION OF HUMAN FIBROBLASTS.

Leavitt J, Goldman D, Merril C, Kakunaga T
Linus Pauling Inst. Science and Medicine, Palo Alto, CA, 94306
Carcinogenesis; 3(1):61-70 1982

The modulation of gene expression accompanying neoplastic transformation has been assessed by computerized microdensitometry of autoradiographic patterns of [35S]methionine labeled polypeptides separated by two-dimensional polyacrylamide gel electrophoresis. Nearly 1,000 polypeptide species of parent diploid human fibroblasts (KD strain) and clonally-derived malignant fibroblast (HUT-14 strain) were compared. HUT-14 fibroblasts express a mutation in one of the two functional beta-actin genes and possess properties that distinguish them as neoplastic cells. Of the 700 more abundant polypeptides measured, 13 were lost and 14 were gained following this neoplastic transformation. It is estimated that less than or equal to 2% of the genes expressing abundant polypeptides were either activated or shut off, but at least 32% were modulated quantitatively as a consequence of this neoplastic transformation. Classes of 'highly variable' and 'marginally variable' polypeptides were assigned. Among the 'highly variable' polypeptides, two related species barely detectable in KD parental cells were synthesized at a 25-31-fold higher rate in the transformed cells, and the cell-associated and extracellular matrix forms of fibronectin were each diminished by greater than 90%. Principles emerging from this study may form a basis for interpretation of the role of individual genes in the expression of neoplastic characteristics in HUT-14 cells. (Author abstract) (29 Refs)

10. CHEMICAL CARCINOGENS TRANSFORM BHK CELLS BY INDUCING A RECESSIVE MUTATION.

Bouck N, Di Mayorca G
Dept. Microbiology/Immunology, Northwestern Univ., Chicago, IL, 60611
Mol Cell Biol; 2(2):97-105 1982

Mechanisms of transformation (TF) by chemical carcinogens were studied in the baby hamster kidney cell line BHK-21 clone 13. Tumorigenic transformed cell lines were derived from BHK cells by exposure to papovavirus (PV), dimethylnitrosamine (DMN), nitrosomethylurea (NMU), or 4-nitroquinoline-N- oxide (4-NQO) or by spontaneous transformation. NMU or 4-NQO produced TF and mutations to 6-thioguanine-resistance (6-TGR) or ouabain-resistance (OR) in a dose-related fashion. Parallel dose-response curves for TF, 6-TGR, and OR suggested that TF and mutation occurred by similar mechanisms. Two frame-shift mutagens, ICR-170 and ICR-191, had dose-response curves for survival and TF that were identical. Both compounds produced temperature-restriction mutations in inverse proportion to frame-shift mutations. Fusion of transformed cells with isogeneic normal cells showed that TF induced by PV behaved as a genetic dominant, but spontaneous or chemically induced TF behaved as a genetic recessive. These genetic patterns were exhibited soon after fusion and also after establishment of hybrid clones. All hybrids were nearly tetraploid. Hybrids showed segregation of TF; transformed phenotype was reexpressed in most cases in the form characteristic of the original transformed parent. Results indicate that chemical carcinogenesis in BHK cells involves induction of a recessive mutation as part of a multistage process. (58 Refs)

11. A 53-KILODALTON PROTEIN COMMON TO CHEMICALLY AND VIRALLY TRANSFORMED CELLS SHOWS EXTENSIVE SEQUENCE SIMILARITIES BETWEEN SPECIES.

Jornvall H, Luka J, Klein G, Appella E
Dept. Chemistry I, Karolinska Institutet, S-104 01 Stockholm, Sweden
Proc Natl Acad Sci USA; 79(2):287-291 1982

A heat-stable DNA-binding protein with subunits of about 53 kilodaltons (kDal) was purified from two virally transformed human cell lines (Epstein-Barr virus-positive Raji and Namalwa) and two mouse tumor cell lines (methylcholanthrene-induced Meth A sarcoma and TA3 mammary carcinoma). All four 53-kDal proteins showed closely related total amino acid compositions, similar peptide maps, and identical NH2-terminal amino acid sequences for 20 residues. These 53-kDal proteins are therefore evolutionarily highly conserved, independent of whether they originate from virally or chemically transformed cells. The NH2-terminal sequence and the protein chain as a whole are not hydrophobic; however, some unexpected residue distributions were observed. Comparisons with other proteins reveal no clear sequence similarity with known tumor antigen structures, homologous immunoglobulins, or some other proteins of known sequence. Epstein-Barr virus-determined nuclear antigen also appears to have a different NH2-terminal sequence. Thus, the results show that the 53-kDal proteins represent a unique protein type with little species variation; this finding suggests that these proteins must perform an important common function in different transformation systems. (Author abstract) (38 Refs)

12. CYTOSOLIC MALIC DEHYDROGENASE ACTIVITY IS ASSOCIATED WITH A PUTATIVE SUBSTRATE FOR THE TRANSFORMING GENE PRODUCT OF ROUS SARCOMA VIRUS.

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Proc Natl Acad Sci USA; 79(2):228-232 1982

A cellular protein of apparent Mr 34,000-36,000 was suggested as a possible physiological substrate for the protein kinase (EC 2.7.1.37) activity associated with the transforming gene product of Rous sarcoma virus. We find this protein to migrate with an apparent Mr of 38,000 in NaDodSO4/polyacrylamide gels. It was not separable from cytosolic malic dehydrogenase activity when purified by chromatography on DEAE-Sephacel, hydroxylapatite, poly(A)-Sepharose, and blue Sepharose, by gel filtration, and by isoelectric focusing. The Mr 38,000 protein as well as cytosolic malic dehydrogenase activity focused with a pI of 7.5. In gel filtration experiments, both displayed an apparent native Mr of 68,000. The malic dehydrogenase activity contained in homogeneous preparations of the Mr 38,000 protein had a specific activity of up to 130 units/mg of protein. The recovery of the enzyme was 5-10% of the activity in the extract. Antiserum against the Mr 38,000 protein inactivated the malic dehydrogenase activity associated with the Mr 38,000 protein. (Author abstract) (43 Refs)

13. BIOCHEMICAL CHARACTERIZATION OF PROTEIN KINASE ACTIVITIES ASSOCIATED WITH TRANSFORMING GENE PRODUCTS OF THE SNYDER-THEILEN AND GARDNER-ARNSTEIN STRAINS OF FELINE SARCOMA VIRUS.

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Lab. Viral Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Virology; 117(1):165-172 1982

Translation products of the genomes of the Snyder-Theilen (ST) and Gardner-Arnstein (GA) feline sarcoma viruses (FeSV) have been shown to possess associated protein kinase activities. These activities are similar to those associated with a number of rapidly transforming retroviruses in that they appear to mediate transfer of radiolabel from [gamma-32P]ATP to selected tyrosine residues in substrates and to be independent of the effects of cAMP and cGMP in vitro. The FeSV activities, when detected in specific immune complexes bound to Staphylococcus aureus, result predominantly in autophosphorylation of FeSV polyproteins. Partially purified polyprotein also induces phosphorylation of an exogenous acceptor (casein) in a soluble protein kinase assay system. The FeSV enzymes display marked preference for Mn++ and Co++ over Mg++ while Ca++ fails to initiate activity in vitro. The optimal pH for the reactions is near 7.0. There is a strict requirement for ATP as phosphoryl donor. High concentrations of ADP and dADP are inhibitory to the reaction but low concentrations of dADP are stimulatory. A comparison of these properties with those of other retroviral-associated protein kinases suggests that these activities fall into three, and possibly four, classes. (Author abstract) (52 Refs)

14. BACTERIAL EXPRESSION OF AN ENZYMATICALLY ACTIVE PROTEIN ENCODED BY RSV SRC GENE.

McGrath JP, Levinson AD
Dept. Molecular Biology, Genentech, Incorporated, 460 Point San Bruno Blvd., South San Francisco, CA, 94080
Nature; 295(5848):423-425 1982

A bacterial plasmid was constructed which is capable of expressing in Escherichia coli a protein (p60) closely related in size and immunological properties to a 60,000-molecular wt (Mr) phosphoprotein (pp60src). The p60 protein appeared to be the translational product of the src gene under the control of the trp promoter. Total cellular proteins were analyzed in E coli transformed with recombinant vector pBR322, pHGH207-1, or pSRCex16. No overall change in the protein profile occurred in cells transformed with pBR322. In cells transformed with pHGH207-1, a prominent protein of 22,000 Mr appeared. Only in pSRCex16-transformed cells, was a 60,000 Mr p60 protein induced; p60 appeared selectively during late growth phase. When induced, p60 represented approx 5% of total bacterial protein. Further characterization of the protein was performed. Protein kinase (PK) activity was assayed in recombinant E coli strain harboring either pBR322 or the p60 expression plasmid (pSRCex16). PK activity was present only in bacteria expressing p60; PK activity, when expressed, was tyrosine-specific. The finding of a tyrosine-specific PK activity in a highly purified bacterially-derived preparation of p60 lended support to the conclusion that this enzymatic activity represents an intrinsic property of the molecule. (35 Refs)

15. EXPRESSION OF TRANSFORMING REGION OF MOLONEY MURINE SARCOMA VIRUS IN ESCHERICHIA COLI AS A FUSION PROTEIN WITH SMALL TUMOR ANTIGEN OF POLYOMA VIRUS.

Donoghue DJ, Hunter T
Tumor Virology Lab., The Salk Inst., P.O. Box 85800, San Diego, CA, 92138
Proc Natl Acad Sci USA; 79(3):800-804 1982

Bacterial expression of the transforming region of Moloney murine sarcoma virus, designated mos, was obtained as a fusion protein with a portion of the small tumor antigen of polyoma virus. This was accomplished by fusing the entire mos open reading frame, encoding a 41,000-dalton protein, with a plasmid that expresses a beta-galactosidase-polyoma fusion protein under lac operon control. The resulting plasmid directed synthesis of the predicted polyoma antigen-sarcoma virus fusion protein of 59,000 daltons. This protein was immunoprecipitated by an antipolyoma tumor antigen antiserum that recognized polyoma determinants at the NH2 terminus of the hybrid protein. This protein was also immunoprecipitated by an antiserum directed against a synthetic peptide containing the 12 COOH-terminal amino acids encoded by the mos open reading frame. This work confirms the existence of a long open reading frame in the mos gene and resolves a discrepancy between different nucleotide sequences for its COOH-terminal coding region. (Author abstract) (32 Refs)

16. GASTRIN AND THE TRANSFORMING PROTEIN OF POLYOMA VIRUS HAVE EVOLVED FROM A COMMON ANCESTOR.

Baldwin GS
Melbourne Tumour Biology Unit, Melbourne, Australia
FEBS Lett; 137(1):1-5 1982

While gastrin and the transforming protein (middle T antigen) of polyoma virus appear to be superficially dissimilar molecules, a hitherto unreported structural relationship between the two proteins is presented, which supports the hypothesis that they have evolved from a common ancestor. (54 Refs)

17. SPECIFIC INTERACTION OF THE SV40 T ANTIGEN-CELLULAR P53 PROTEIN COMPLEX WITH SV40 DNA.

Reich NC, Levine AJ
(c/o Levine) Dept. Microbiology, State Univ. New York Stony Brook, Sch. Medicine, Stony Brook, NY, 11794
Virology; 117(1):286-290 1982

Three forms of the simian virus 40 (SV40) large tumor antigen (T antigen), free T antigen from infected monkey cells, T antigen-p53 complex from virus-infected mouse cells, and T antigen-p53 complex from SV40-transformed mouse cells, were examined for their abilities to bind specifically to SV40 DNA. Employing an immunoassay that detected T antigen and/or p53 protein bound to restriction fragments of viral DNA, it was shown that all three of these forms of SV40 T antigen bind preferentially to the restriction fragment of SV40 DNA containing the nucleotide sequence at the origin of viral DNA replication. Free p53 protein alone failed to bind to SV40 DNA in this assay. These results indicate that the SV40 T antigen-p53 protein complex displays the same SV40 DNA binding specificity as free T antigen obtained from a productive infection. (Author abstract) (24 Refs)

18. RESOLVING THE FUNCTIONS OF OVERLAPPING VIRAL GENES BY SITE-SPECIFIC MUTAGENESIS AT A MRNA SPLICE SITE.

Montell C, Fisher EF, Caruthers MH, Berk AJ
Dept. Microbiology, Univ. California, Los Angeles, CA, 90024
Nature; 295(5848):380-384 1982

Early region IA of human adenoviruses encodes a function required for normal induction of early viral genes and virus-induced cell transformation. The region is expressed at early times as two overlapping spliced mRNAs, 12S and 13S, which encode closely related proteins. To distinguish between the functions of these proteins, a single T to G transversion was constructed which prevents splicing of the 12S mRNA. This transversion, in the second base of the 12S mRNA intron, does not alter the protein encoded by the 13 mRNA due to degeneracy in the genetic code. Studies with this mutant demonstrated that only the 13S mRNA encodes the regulatory protein required for normal early gene expression. (Author abstract) (47 Refs)

19. INTEGRATION AND EXPRESSION OF VIRAL DNA IN CELLS TRANSFORMED BY HOST RANGE MUTANTS OF ADENOVIRUS TYPE 5.

Ruben M, Bacchetti S, Graham FL
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J Virol; 41(2):674-685 1982

Group I host range (hr) mutants of adenovirus Type 5 are unable to transform rat embryo or rat embryo brain cells but induce an abnormal transformation of baby rat kidney cells. We established several transformed rat kidney cell lines and characterized them with respect to the transformed phenotype and the structure of the integrated viral DNA. The hr mutant-transformed cells, unlike wild-type virus transformants, were fibroblastic rather than epithelial, failed to grow in soft agar, and were also less tumorigenic in nude mice. Studies on the structure of the integrated viral DNA sequences showed that hr-transformed cells always contained the left end of the adenovirus DNA, but the size of the integrated DNA fragment varied among different lines, and a high percentage of the lines contained the entire viral genome colinearly integrated. The patterns of integration were maintained after prolonged growth in culture and after subcloning. Attempts to rescue infectious virus from lines which contained the entire genome were unsuccessful. Using immunoprecipitation and sodium dodecyl sulfate-polyacrylamide gel electrophoresis, we analyzed the viral proteins expressed in hr-transformed cells. Results of these studies indicated that, like wild type-transformed cells, hr transformants expressed E1B proteins of mol wt 58,000 and 19,000. (Author abstract) (48 Refs)

GENETIC AND OTHER HOST FACTORS WHICH MODULATE ONCOGENIC TRANSFORMATION

20. INFLUENCE OF ATAXIA TELANGIECTASIA GENE DOSAGE ON BLEOMYCIN-INDUCED CHROMOSOME BREAKAGE AND INHIBITION OF REPLICATION IN HUMAN LYMPHOBLASTOID CELL LINES.

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Exp Cell Res; 137(2):387-395 1982

Long-term lymphoblastoid cell lines, obtained by E-B virus transformation of peripheral blood lymphocytes, retain many of the features of hypersensitivity to environmental agents found in primary cultures and fibroblast strains from patients with genetic diseases. Primary lymphocyte cultures from patients with ataxia telangiectasia, a cancer-prone genetic disease, have increased sensitivity to chromosomal damage induced by the radio-mimetic drug, bleomycin. In order to study the expression of ataxia telangiectasia gene dosage in lymphoblastoid cell lines, we examined chromosomal aberrations in lines containing two, one, or no alleles for ataxia telangiectasia obligate heterozygotes, and from presumably normal donors, respectively. Chromosome preparations were made 46 hr after a 2 hr exposure to bleomycin and scored for chromosome breakage, for the relative rate of cell replication as assessed by sister chromatid differentiation patterns, and for the frequency of sister chromatid exchanges. Baseline frequencies of chromosome breakage and sister chromatid exchanges, and baseline rates of cell replication were similar in all nine lymphoblastoid cell lines. Following treatment with 25 or 250 mU/ml bleomycin, all the lymphoblastoid cell lines showed increased chromosome breakage and decreased cell replication. The lymphoblastoid cell lines from the ataxia telangiectasia homozygotes had significantly increased chromosome breakage and decreased rate of cell replication after either bleomycin dose in comparison with the normal or with the ataxia telangiectasia heterozygous lines. Sister chromatid exchange frequencies were not altered by bleomycin exposure. (Author abstract) (31 Refs)

21. THE MECHANISM OF GENETIC RESISTANCE TO MAREK'S DISEASE IN CHICKENS.

Powell PC, Lee LF, Mustill BM, Rennie M
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Int J Cancer; 29(2):169-174 1982

Genetic resistance to Marek's disease in RPL line-6 chickens is expressed not only at the level of host immunological responses against virus and tumor antigens, but also at the level of target lymphoid cells for virus infection and transformation. The nature of the target cell involved was investigated. Spleen cells from susceptible line-7 chickens adsorbed more Marek's disease virus and turkey herpesvirus in vitro than line-6 spleen cells. In the case of Marek's disease virus this was reflected in the replicative ability of the virus in vivo. Transplantation of thymus fragments from 1-day-old line-7 chickens into thymectomized line-6 chickens conferred a high degree of susceptibility on the latter, but the transplantation of spleen or bursa fragments had no significant effect. The reverse procedure, ie grafting of line-6 thymi into line-7 chickens, did not diminish the susceptibility of the recipients. In each treatment group the observed titers of leukocyte-associated viremia correlated with the susceptibility of the group to Marek's disease. Histologically the grafted thymus fragments became depleted of lymphocytes immediately after transplantation. By 6 days there was substantial recovery, apparently as a result of repopulation of the thymic epithelium by host stem cells. This was confirmed by transplanting thymus fragments between individuals of opposite sexes. Karyotype analysis showed that the thymus contained lymphocytes of the sex of the recipient. However, karyotype analysis of lymphoma cells taken from recipient line-6 chickens that had received thymus grafts from line-7 birds of the opposite sex showed that, in the majority of cases, the lymphomas consisted of cells of donor origin. It is concluded that the susceptibility of line-7 chickens is largely attributable to the greater susceptibility of their T-lymphocytes to infection and transformation by Marek's disease virus, and that this susceptibility can be transferred to genetically resistant line-6 birds by adoptive transfer of the cells in the form of thymus fragments. (Author abstract) (16 Refs)

22. INFLUENCE OF ONCOGENICITY OF MAREK'S DISEASE VIRUS ON EVALUATION OF GENETIC RESISTANCE.

Schat KA, Calnek BW, Fabricant J, Abplanalp H
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Poult Sci; 60(12):2559-2566 1981

Resistance to Marek's disease (MD) was studied in 14 genetically different strains of chickens, all fixed for the major histocompatibility complex except S-strain and PDRC. Nine strains previously characterized, the inbred UCD-003 strain, and four congenic lines were evaluated. The GA-5, JM-10, and RB-1B MD virus strains were used. Chickens were exposed to MD virus at 1, 14, 9, and 2 days of age and were examined for MD on days 81, 58, 70, and 90 or 83, respectively. The five highly resistant cell lines were the N-line, two derivatives from the N-line, PDRC strain, and a congenic UDC line. Moderately resistant lines included the UDC-003 and three other congenic lines. Highly susceptible strains included the S-strain, P-2, and P-5. The N-2 and N-5 lines had a significantly lower GA-5-induced MD incidence than the other cell lines and were significantly more resistant to JM-10 than to GA-5 infections; S-strain and P-2 were susceptible to both virus strains. A newly isolated RB-1B strain of MD virus caused a significantly faster rate of mortality in P-2 than in S-strain chickens and a significant increase in MD incidence in N-2 birds compared to infection with either JM-10 or GA-5. Differentiation of genetic resistance levels was not possible with GA-5 and RB-1B because of the high incidence of MD induced in all cell lines. (22 Refs)

23. RECENT ADVANCES IN CANCER CYTOGENETICS.

Pogosiants EE
All-Union Cancer Res. Center, Moscow, USSR
Genetika; 17(12):2087-2099 1981

Recent studies in the field of cancer cytogenetics are reviewed with special emphasis on karyotypic changes in leukemia and carcinoma cells, prezygotic chromosome mutations specific for certain human tumors, and phenomena of gene amplification characteristic for a number of tumors and for cells resistant to antineoplastic agents. Specific karyotypic changes were observed in human and murine leukemias, as well as in a number of experimental sarcomas and carcinomas. Specific involvement of chromosome 15 was recorded in murine radiation-induced and carcinogen-induced T-cell leukemias; also, trisomy for chromosome 15 or translocation involving chromosome 15 were detected in B-cell leukemias and lymphomas. Specific involvement of the distal third of chromosome 15 indicated that this region contains the cluster of genes responsible for normal differentiation and malignant transformation of lymphoreticular cells. Specific prezygotic chromosome aberrations were observed in retinoblastoma (deletion in the long arm of chromosome 13), nephroblastoma (deletion in the short arm of chromosome 11), and in familial kidney carcinoma (translocation between chromosomes 3 and 8). Specific resistance of eukaryotic cells to methotrexate was shown to be associated with the presence of homogenously stained regions and the number of double microchromosomes. (73 Refs) (In RUS)

24. PROCANCER CLASS OF GENES AND GENERATION OF CHROMOSOME MUTATION.

Sasaki MS, Ejima Y
Radiation Biology Center, Kyoto Univ., Yoshida-konecho, Sakyo-ku, Kyoto 606, Japan
Gann Monogr Cancer Res; 27:85-94 1982

The nature of inherent mutation associated with chromosome instability and high cancer risks is discussed. Human genetic syndromes associated with chromosome instability include Fanconi's anemia (FA), ataxia telangiectasia (AT), Bloom's syndrome (BS), incontinentia pigmenti (IP), and, perhaps xeroderma pigmentosum (XP). Chromosome aberrations are primarily of the chromatid type, indicating that the chromosome mutations in these diseases arise in connection with DNA replication. FA, AT, and IP have a significantly high frequency of chromosome aberrations, while the other diseases show normal aberration rates. DNA damage left unrepaired in AT and FA cells might not be subject to repair by post-replication error-prone repair mechanisms or such a mechanism might not operate in these cells. Genetically-determined cancer proneness appears to be caused by an intrinsic sensitivity of instability to chromosome mutation; gross chromosomal change is a prime importance in mutation toward cancer. Certain types of procancer genes with dominant traits express a mutator function and promote chromosome recombination in their somatic cells. Such mutations of de novo origin occur in familial polyposis coli, Gardner's syndrome, Peutz-Jegher's syndrome, nevoid basal cell carcinoid syndrome, hereditary retinoblastoma, dominantly-inherited familial leukemia, and familial colon cancer. The nature of germinal mutations responsible for organ-specific cancer proneness is discussed. (37 Refs)

EXPERIMENTAL MODULATION OF ONCOGENIC TRANSFORMATION

25. EFFECTS OF PHORBOL ESTERS ON FETAL RAT EPIDERMAL CELLS IN CULTURE.

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Gann Monogr Cancer Res; 27:145-158 1982

Effects of 12-O-tetradecanoyl-phorbol-13-acetate (TPA) on aneuploid nonmalignant fetal rat epidermal cells (FRSK-2 cells) were investigated. TPA inhibited cell proliferation at concentrations above 1 nanog/ml, while a stimulating effect was noted at concentrations of 0.01-0.1 nanog/ml after 24 hr. The inhibitory effect continued at 72 and 120 hr, while the stimulatory effect at low concentrations was not observed. TPA inhibited keratinization of lamellar processes of many aneuploid premalignant epidermal cell lines, but did not inhibit keratinization of malignant epidermal cell but destroyed the polarity retained in their keratinization processes. Two-stage treatment of FRSK-2 cells with benzo[a]pyrene (BP; 1 ug/ml for 1, 2, 7, or 14 days), then maintained in TPA-containing medium (1, 10, 100, and 1,000 nanog/ml) for 10 wk is reported. BP treatment for up to 2 wk did not induce any noticeable changes in the cells. However, BP treatment for 2 wk at 1 ug/ml resulted in stimulation of keratinization. TPA treatment severely inhibited the growth of FRSK-2 cells, even after BP treatment. Atypical cells were observed at 14-62 days after the beginning of TPA treatment. The changes induced in FRSK-2 cells by the two-stage treatment were irreversible. TPA treatment increased the plating efficiency of BP-treated cells. Following treatment with BP and TPA, the major characteristics of the cells included shortened generation time, acquisition of high plating efficiency values, and abnormal keratinization processes and growth on the agar surface; comparable with changes accompanying malignant transformation of fetal rat epidermal cells. (50 Refs)

26. REVERSAL OF THE PROMOTIONAL EFFECT OF 12-O-TETRA-DECANOYLPHORBOL-13-ACETATE ON MORPHOLOGICAL TRANSFORMATION OF HAMSTER EMBRYO CELLS BY GLUCOCORTICOIDS.

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Norwegian Radium Hosp., Montebello, Oslo 3, Norway
Cancer Lett; 15(2):105-113 1982

Effects of glucocorticoids and cholesterol on morphologic transformation by benzo(a)pyrene (BP) and 12-O-tetradecanoylphorbol-13-acetate (TPA) in hamster embryo cells were studied. Cells exposed to BP (0.05 ug/ml) during the first 3 days of incubation (period 1) and then to TPA (0.05 ug/ml) during the last 3 days (period 2) had a transformation frequency of 10.2%. When present during period 2, hydrocortisone and dexamethasone strongly inhibited the formation of transformed colonies. Corticosterone had only a slight inhibitory activity and cortisone had no inhibitory activity when administered in concentrations up to 25 uM. Dexamethasone, the most potent glucocorticoid, reduced transformation frequency by greater than 50% at 0.25 nanoM and completely abolished transformation at 250 nanoM. Cholesterol (2.5 or 25 uM) increased transformation frequency. The glucocorticoids had no effect when present only during period 1. The fact that addition of dexamethasone (250 nanoM) reduced transformation frequency even when added 6 hr before staining suggested that glucocorticoids rapidly reverse the morphology of transformed colonies back to normal. (31 Refs)

27. ISOLATION FROM MURINE SARCOMA CELLS OF NOVEL TRANSFORMING GROWTH FACTORS POTENTIATED BY EGF.

Roberts AB, Anzano MA, Lamb LC, Smith JM, Frolik CA, Marquardt H, Todaro GJ, Sporn MB
Lab. Chemoprevention, NCI, NIH, Bethesda, MD, 20205
Nature; 295(5848):417-419 1982

Two distinct classes of intracellular transforming growth factors (TGF) were isolated from Moloney sarcoma virus (MSV)-transformed 3T3 cells. One TGF competed with epidermal growth factor (EGF) for receptor binding sites, whereas the other did not. After high-performance liquid chromatography purification, the colony-forming activity of the TGF that do not compete with EGF for receptor binding was enhanced 100-fold by the addition of EGF. The abiliity to enhance growth-stimulating effects of TGF was specific for EGF, as insulin, the insulin-like growth factors, platelet-derived growth factor, and nerve growth factor did not show this property. In contrast, the colony-forming activity of TGF that compete with EGF for receptor binding was not potentiated by EGF. The role of the new TGF in malignant transformation, wound repair, and embryogenesis are discussed. (24 Refs)

28. MORPHOLOGICAL TRANSFORMATION OF CELLS INDUCED BY KIRSTEN SARCOMA VIRUS TRANSFORMING FACTOR IS INDEPENDENT OF SERINE PROTEASES.

Fulton RJ, Kaplan PL, Hart DA, Ozanne B
(c/o Ozanne) Dept. Microbiology, Univ. Texas Health Science Center at Dallas, Dallas, TX, 75235
J Cell Physiol; 110(1):81-83 1982

Kirsten murine sarcoma virus (MSV)-induced cell transformation is though to be regulated by a low mol wt peptide growth factor(s) known as transforming factor (TF) which is extractable from MSV-transformed NRK cells' conditioned medium. A caseinolytic assay was used for detection of neutral protease and plasminogen activator (PA) activities in extracted TF and in fully-transformed Rat-1 cells which had been treated with TF. Neither the isolated TF nor the cultures of Rat-1 cells showed elevated protease or PA activities; neutral proteases and PA evidently do not play a role in the morphological transformation induced by TF. (15 Refs)

29. ADENOVIRUS-CELL INTERACTIONS EARLY AFTER INFECTION: IN VITRO CHARACTERISTICS AND TUMOURIGENICITY OF ADENOVIRUS TYPE 2-TRANSFORMED RAT LIVER EPITHELIAL CELLS.

Paraskeva C, Brown KW, Gallimore PH
Imperial Cancer Res. Fund, P. O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England
J Gen Virol; 58(part1):73-81 1982

Cloned rat liver epithelial cells (clone C3) were semi-permissive for adenovirus type 2 (Ad-2) and non-permissive for adenovirus type 12 (Ad-12). Ad-2-infected C3 cells were shown to produce hexon and fiber protein, but at an moi of 20 a maximum virus yield of only 2.4 pfu per cell was obtained. Forty-eight hr after infection with Ad-12 'early' virus proteins (major species 8K and 60K), but no 'late' proteins (virus structural proteins) could be identified. Of six Ad-2-transformed epithelial lines isolated from clone C3 only one was tumorigenic in syngeneic rats, whereas all six transformants produced tumors in athymic nude mice. There was a remarkable variation in the morphology of the Ad-2-transformed liver cells, ranging from an epithelial morphology similar to C3 cells to cells with a distinct lymphoid morphology. The in vitro and in vivo behavior of the Ad-2-transformed clone C3 cells reported in this communication, taken together with our previous report on the characteristics of Ad-12-transformed C3 cells, clearly show that the differences observed between Ad-2-and Ad-12-transformed rat embryo cells were also observed in our studies using cloned rat liver epithelial cultures. Our findings clearly rule out the hypothesis that the heterogeneity of Ad-2 transformation events is the result of the transformation in vitro of different types of target cell. (Author abstract) (23 Refs)

30. MALIGNANT TRANSFORMATION OF CELLS OF NEWBORN HAMSTERS BY HERPES SIMPLEX VIRUS TYPE 2.

Kitsak VIa
Central Inst. Advanced Training for Physicians, Moscow, USSR
Vopr Virusol; (6):750-753 1981

Malignant transformation induced by herpes simplex virus Type 2 (HSV-2) was studied in cultured fibroblasts from 3-5 day old hamsters. Infection of primary culture with UV-inactivated HSV-2 caused morphological transformation of cells; first signs of morphological transformation were detected 14-25 days after infection. Characteristic features of morphological transformation were the loss of contact inhibition, multilayer growth, and progressive replacement of epithelioid cells by fibroblastlike cells. Immunofluorescent analysis showed the presence of virus-specific antigen in 5-30% of transformed cells, but transformed cells did not produce the infectious virus. Syngeneic newborn hamsters inoculated sc with transformed cells developed fibrosarcomas. Duration of the latent period was correlated with the number of passages in vitro (from 12 wk after 27 passages to 4 wk after 50 passages). (11 Refs) (In RUS)

31. NEOPLASTIC TRANSFORMATION OF SYRIAN HAMSTER EMBRYO CELLS BY BISULFITE IS ACCOMPANIED WITH A DECREASE IN THE NUMBER OF FUNCTIONING REPLICONS.

Doniger J, O'Neill R, DiPaolo JA
Lab. Biology, NCI, Bethesda, MD, 20205
Carcinogenesis; 3(1):27-32 1982

Bisulfite, a chemical that at neutral pH does not induce mutations at two loci in Chinese hamster V-79 cells, induces transformation of Syrian hamster embryo cells. Although bisulfite affects DNA metabolism, there was no evidence of bisulfite-induced DNA damage. Bisulfite induced no excision repair replication, caused no DNA strand breaks detectable in alkaline sucrose gradients, had no effect on the size distribution of DNA nascent daughter strands, and did not affect excision on post-replication repair of uv-induced damage. However, bisulfite did induce a dose-dependent decrease in the rate of DNA replication per cell, apparently due to a reduction in the number of functioning replicons. Since the data indicate that bisulfite causes no detectable DNA damage, it appears that bisulfite induces transformation by a non-mutagenic event that could involve the inhibition of semi-conservative DNA synthesis. (Author abstract) (27 Refs)

32. THE MYELOPROLIFERATIVE SARCOMA VIRUS CAUSES TRANSFORMATION OF ERYTHROID PROGENITOR CELLS IN VITRO.

Hankins WD, Kost TA, Pragnell IB
(c/o Pragnell), Beatson Inst. for Cancer Res., Bearsden, Glasgow, G61 1BD, Scotland
Mol Cell Biol; 2(2):138-146 1982

In vitro transformation of mouse erythroid progenitor cells by myeloproliferative sarcoma virus (MPSV) was studied. Anemia was induced in male BALD/c, DBA/2J, C57BL/6, and CD2F1 mice by injection of phenylhydrazine hydrochloride (PHZ: 40 ug/g, days 1, 2 and 4). Bone marrow or spleen cells from PHZ-treated mice were cultured with or without erythropoietin (EPO: 0.2 units/ml) The presence of Hb was measured by benzidine staining. Cultures treated with EPO showed a transient increase in Hb-containing cells at days 2-3, lysis of erythroid cells on day 4, and few, if any, erythroid cells by day 5. Cultures infected with MPSV without EPO showed a few erythroid bursts (EB) on days 5-9. Addition of 0.1 unit EPO/ml to MPSV-infected cultures resulted in a significant increase in EB. The number of EB was related to the amount of virus present during absorption. MPSV induced EB in spleen cells from all mouse strains tested, with greatest effect on CD2F1 cells. The greatest numbers of EB were present on days 6-8 after infection. Predominant cell fractions consisted of large proerythroblast-like cells on days 3-5, smaller Hb-containing cells on days 6-7, and nucleated erythrocytes and reticulocytes on days 8-10. Assays using a number of factors indicated that EB-inducing activity was produced by MPSV, rather than by a soluble factor. The activity was eliminated by heat treatment or sedimentation. (33 Refs)

33. IN VITRO STUDIES OF THE MECHANISM OF LEUKEMOGENESIS. II. CHARACTERIZATION OF ENDOGENOUS MURINE LEUKEMIA VIRUSES ISOLATED FROM AKR THYMIC EPITHELIAL RETICULUM CELL LINES.

Yanagihara K, Hamada K, Seyama T, Imamura N, Yokoro K
Dept. Pathology, Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Hiroshima, Japan
J Virol; 41(2):360-366 1982

Thymic epithelial reticulum (TER) cell lines were established from thymuses of a young healthy AKR mouse (A2T), a preleukemic AKR mouse (A6T), and two lymphoma-bearing AKR/Ms mice (ASLT-1 and ASLT-2). Numerous Type-C virus particles with occasional budding forms were observed in all cell lines. Expression of XC-detectable, N-tropic, ecotropic virus was observed in every cell line, whereas the presence of xenotropic and mink cell focus-inducing (MCF) viruses could be detected only in TER cells derived from preleukemic and leukemic mice. Expression of xenotropic virus in various cells of newborn and young AKR mice could readily be induced by IUdR treatment, whereas MCF virus was never detected in these cells, with the exception of the A2T cell line after more than 20 passages, in which MCF virus with dual-tropic infectivity emerged in addition to ecotropic and xenotropic viruses. These spontaneous and induced MCF viruses were purified, and their virological properties were characterized. The cloned MCF viruses (MCFs AT1, AT2, AT3, and AT4-IU) showed dual tropism and produced cytopathic effect-like foci in mink lung cells. Preinfection with either ecotropic or xenotropic virus interfered with the infectivity of MCF viruses. Spontaneous leukemogenesis in AKR mice was accelerated by the inoculation of MCF viruses. These findings indicate that TER cells could serve as the host cells for the genetic recombination of the endogenous MuLV; the recombinant MuLV, MCF virus, appears to be most closely associated with leukemogenesis in AKR mice. (Author abstract) (29 Refs)

34. CELL TRANSFORMATION, MUTATION, AND CANCER.

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Gann Monogr Cancer Res; 27:195-206 1982

The abilities of 2-aminopurine (AP) and diethylstilbestrol (DES) to induce neoplastic transformation and/or somatic mutation in Syrian hamster embryo cell assays was investigated. AP is a well-defined mutagen and an inactive carcinogen, while DES is a known carcinogen and is inactive as a mutagen. AP was shown to be, at best, a weak transforming agent. DES failed to induce measurable somatic mutations at either of the two loci tested. At the chromosome level, a mutation is one cause of morphological transformation and possibly cancer. Chromosome changes are very early manifestations of a neoplastic alteration and may be an initial part of neoplastic development in vivo. A theory on the relationship between tumor initiation, differentiation, and chromosome mutations is proposed. The carcinogen induces chromosome mutations, gene mutations, and nonmutational changes, any of which might lead to neoplastic development. The most frequent event results from a chromosome mutation which prevents normal cellular differentiation, thereby providing a selective growth advantage for the altered cells. The altered cell grows and mutational or nonmutational secondary changes may occur. (63 Refs)

35. POTENCY RANKING OF CHEMICALS BASED ON ENHANCEMENT OF VIRAL TRANSFORMATION.

Casto BC
Northrop Services, Inc., Research Triangle Park, NC
Potency Ranking of Chemicals Based on Enhancement of Viral Transformation. Avail able from National Technical Information Service, Springfield, VA, as PB81-210080:, 41 pp., 1981.

Treating primary hamster embryo cells with various classes of chemical carcinogens and mutagens leads to enhancement of transformation by simian adenovirus SA7. It appears that carcinogenic chemicals render the individual cells more sensitive to viral transformation, thus increasing the total number of cells integrating SA7 DNA. Enhancement of viral transformation appears to be a sensitive indicator for chemical agents with the potential to damage cell DNA by either direct or indirect means and thus may be useful as a screening tool to detect these chemicals in the environment. This report summarizes and compares the results for 134 chemicals (both carcinogenic and noncarcinogenic) assayed for enhancement of SA7 transformation, chemical transformation, and induction of DNA strand breaks and DNA repair synthesis. In addition, these chemicals are ranked by lowest effective concentration in the assay for enhancement of viral transformation. (Author abstract)

BIOCHEMICAL AND MOLECULAR BIOLOGICAL STUDIES OF TRANSFORMED PHENOTYPE

36. PHOSPHORYLATION OF A 36,000 MR CELLULAR PROTEIN IN CELLS INFECTED WITH PARTIAL TRANSFORMATION MUTANTS OF ROUS SARCOMA VIRUS.

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Mol Cell Biol; 2(2):147-153 1982

Correlation of parameters of transformation with phosphorylation of the phosphoprotein pp60src in cell infected with mutants of Rous sarcoma virus (RSV) was studied. Chick embryo fibroblasts were infected with viruses derived from the Schmidt-Ruppin strain of RSV, subgroup A. Viruses tested included wild-type (WT), temperature-conditional mutants (tsGI251, tsCU11, and tsNY68), CU2 mutant, and fusiform CU12 mutant. The mutant strains induced some, but not all, parameters of cellular transformation. The 36,000 mol wt pp60src from uninfected fibroblasts showed little or no phosphorylation. Equivalent pp60src from RSV-infected fibroblasts showed phosphorylation. Phosphorylation was temperature-conditional in cells infected with tsNY68, tsCU11, and tsGI251. Cells infected with CU2 showed a low degree of phosphorylation. Pp60src from RSV-infected cells was phosphorylated with tyrosine and serine, phosphotyrosine being predominant. Analysis of phosphorylation and occurrence of transformation parameters showed that phosphorylation of pp60src was neither sufficient nor necessary for loss of surface fibronectin or loss of density-dependent inhibition of growth. Phosphorylation was not sufficient but was possibly required for changes in morphology. Phosphorylation was not sufficient for loss of adhesiveness or full increase in hexose transport. Phosphorylation correlated well with increase in plasminogen activator. Results suggest that phosphorylation of pp60src may be required for malignant growth. (23 Refs)

37. TYROSINE PHOSPHORYLATION OF A 50K CELLULAR POLYPEPTIDE ASSOCIATED WITH THE ROUS SARCOMA VIRUS TRANSFORMING PROTEIN PP60SRC.

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(c/o Martin) Dept. Zoology, Univ. California, Berkeley, CA, 94720
Mol Cell Biol; 2(2):199-206 1982

A 50,000 dalton cellular polypeptide (50K-CP) associated with the transforming protein pp60src of the Rous sarcoma virus (RSV) was studied. 50K-CP from cells that were uninfected or infected with a transformation-defective RSV contained phosphoserine but little or no phosphotyrosine (PT). 50K-CP from cells infected by transforming RSV showed a 50-fold increase in PT, indicating that pp60src is required for phosphorylation of 50K-CP at tyrosine. 50K-CP may be a high-affinity substrate of pp60src. (31 Refs)

38. BIOLOGY OF SIMIAN VIRUS 40 (SV40) TRANSPLANTATION ANTIGEN (TRAG). VIII. RETENTION OF SV40 TRAG SITES ON PURIFIED SV40 LARGE T ANTIGEN FOLLOWING DENATURATION WITH SODIUM DODECYL SULFATE.

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Virology; 117(1):267-270 1982

Simian virus 40 (SV40) large tumor (T) antigen was isolated from SV40-infected permissive and -transformed cells by immunoprecipitation with anti-T sera and purified by electrophoresis on solubilizable SDS-polyacrylamide gels. This method proved to be a rapid and efficient procedure for purifying T antigen as 74% of the immunoprecipitated T antigen was subsequently recovered. The purified, SDS-denatured large T antigen retained its ability to react with anti-T antibody and to immunize mice against a challenge of syngeneic SV40 tumor cells, indicating that the antigenic sites present on the large T antigen molecule that induce a tumor rejection response in vivo are resistant to denaturation by SDS. (Author abstract) (25 Refs)

39. ELECTRON SPIN RESONANCE OF GROWING NORMAL AND VIRUS-TRANSFORMED CELLS.

Conti F, Segre AL, Eremenko T, Zaniratti S, Elia G, Benedetto A, Volpe P
Inst. Physical Chemistry, Univ. Rome, Rome, Italy
Cancer Biochem Biophys; 5(3):195-199 1981

A $g = 2.003$ electron spin resonance (ESR) signal, previously detected in association with a free radical in HeLa cells, was analyzed in fractionated HeLa cells and whole cell cultures of mouse embryo 3T3 fibroblasts transformed by Simian virus 40 (SV40) and in normal rabbit kidney (NRK) cells transformed by Rous sarcoma virus (RSV). The $g = 2.003$ ESR signal was localized in the mitochondria and nuclei of HeLa cells and had the same shape in both compartments as in whole cells; no signal was detected from cytoplasmic and membranal compartments. In the other cell lines the signal was maximal in intensity in the lag stage but reduced thereafter; in 3T3 and 3T3/SV40 cells the maximal value occurred early in the lag stage. The max signal occurs late in the lag phase in NRK and NRK/RSV cells. Specific intensity of the $g = 2.003$ ESR signal per cell is significantly higher in 3T3 and 3T3/SV40 cells than in NRK and NRK/RSV cells. Av specific intensity of the ESR signal over the whole culture period is higher in normal cells of both lines, but the maximal point of resonance per cell during the lag stage is higher in the transformed cells. The role of free radicals as triggers in cells grown in vitro is discussed. (10 Refs)

40. TRANSFORMED CELLS EXHIBIT ALTERED RESPONSE TO DB CYCLIC AMP-MEDIATED MODULATION OF PROTEIN PHOSPHORYLATION AND DIFFERENT ENDOGENOUS PHOSPHOPROTEIN ACCEPTORS.

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Cancer Biochem Biophys; 5(3):163-167 1981

Detergent solubilized particulate fractions (DSF) and cytoplasmic fractions (CF) derived from NRK cells transformed with the temperature-sensitive ts24 derivative of Rous sarcoma virus and grown at 33 C (malignant phenotype) and 39 C (normal phenotype) were compared. Protein kinase activities were in the following order: DSF, transformed greater than or equal to DSF, phenotype normal greater than or equal to CF, transformed greater than or equal to CF, phenotype normal. Incubation of CF of morphologically normal cells grown for 48 hr at 39 C with ATP-gamma-32P led to phosphorylation mostly in components of 60,000 and 68,000 daltons; in vitro exposure of extracts to dibutyryl cyclic AMP increased labeling of the 60,000 dalton component and decreased labeling in the 68,000 dalton component. A similar experiment with CF of phenotypically transformed cells grown at 33 C yielded 140,000 and 38,000 dalton components, both of which showed decreased labeling when the experiment was repeated with cyclic AMP preincubation. DSF of phenotypically normal cells labeled preferentially in 38,000, 65,000, and 94,000 dalton regions, and these preferences did not change with cyclic AMP. DSF of phenotypically transformed cells labeled mainly in the 65,000 dalton region; with cyclic AMP preincubation the 65,000 dalton labeling decreased and labeling increased in the 220,000 dalton region. Failure of transformed cells to phosphorylate some substrates may be due to a transformation-induced alteration in the availability of endogenous protein acceptors for the phosphorylation process, and not to a low level of protein kinase activity. (13 Refs)

41. NEURAMINIDASE ACTIVITY AND CELL SURFACE SIALIC ACID TURNOVER IN ROUS SARCOMA VIRUS TRANSFORMED CHICK EMBRYO FIBROBLASTS.

Myers-Robfogel MW, Spataro AC, Bosmann HB, Morgan HR
Dept. Pharmacology and Toxicology, Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY, 14642
Cancer Biochem Biophys; 5(3):141-146 1981

Activities of neuraminidase (Ndase), cytidine monophosphate-N-acetyl neuraminic acid synthetase (CMP-AcNeu synthetase), and cytidine monophosphate-N-acetylneuraminic acid hydrolase (CMP-AcNeu hydrolase) were determined in primary cultures of chick embryo fibroblasts (CEF) transformed with the Schmidt-Ruppin strain of Rous sarcoma virus (RSV) and CEF infected with a Rous-associated virus that did not transform them. Total acid-labile sialic acid (SA) was decreased in RSV-CEF cells, but not in RAV-CEF cells. Ndase-accessible SA was increased above the control levels in both transformed and untransformed infected cells. Total Ndase activity in whole cell homogenates assay by neuraminlactitol-(3H) was elevated at both pH 4.3 and pH 6.8 in RSV-CEF but not in RAV-CEF, and cell-surface Ndase activity was also elevated in RSV-CEF according to release of (14C)-SA from cells preincubated with CMP-(14C)N-acetylneuraminic acid. Transformed and untransformed cells did not differ from controls in activities of CMP-AcNeu synthetase and CMP-AcNeu hydrolase. Ndase activity in the cell and at the cell surface appears important in maintaining the altered SA-containing macromolecules of the transformed cell surface. (16 Refs)

42. SV40-TRANSFORMED HUMAN CELLS FAIL TO GROW IN ZINC CONCENTRATIONS WHICH PERMIT NORMAL HUMAN FIBROBLAST PROLIFERATION.

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J Cell Physiol; 110(1):17-22 1982

The effects of exogenous Zn (ZnSO4) on the growth of normal human foreskin and forearm fibroblasts and four different SV40-transformed human fibroblast cell lines are described. Growth of normal cells was enhanced slightly by Zn at 0.10 and 0.15 milliM (mM), and toxic effects increased with concentration up to 0.30 mM, the highest concentration tested. All Zn levels were inhibitory to transformed fibroblasts, with about a 6-fold range among them in response to 0.175 mM Zn. With only 0.175 mM Zn, normal cells were able to achieve several cell generations, but transformed cells had significantly fewer cells after 4 or 5 days of incubation than when originally plated. Another experiment revealed no detectable effect of plating density (442 cells/square cm to 5,305 cells/square cm) on the toxicity response of transformed cells to either 0.150 mM or 0.175 mM Zn. Fetal bovine serum at 10% of the medium and 20% of the medium showed a protective effect for transformed cells against 0.150 mM ZnSO4. Both transformed and normal fibroblasts had a low level of Zn-binding protein in medium lacking Zn, and both produce approx the same amount of Zn-binding protein (probably metallothionein) in the presence of ZnSO4. Biological activity of the metallothionein(s) of transformed cells may explain the toxic effect, but further studies are necessary to confirm the precise mechanism of Zn toxicity in the cells. (25 Refs)

43. DECREASED UPTAKE AND RETENTION OF RHODAMINE 123 BY MITOCHONDRIA IN FELINE SARCOMA VIRUS-TRANSFORMED MINK CELLS.

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Cell; 28(1):7-14 1982

A reduced uptake and retention of the mitochondria-specific membrane potential probe rhodamine 123 by feline sarcoma virus (FeSV)-transformed mink fibroblasts (64F3) has been detected. The decreased accumulation of rhodamine 123 by 64F3 mitochondria is not due to abnormal plasma membrane dye permeability, since after microinjection of the dye these cells are still unable to retain the dye at levels comparable to the untransformed parental cells, CCL 64. Nigericin, an ionophore that mediates an electrically neutral exchange of protons of potassium ions resulting in the elimination of the pH gradient across the mitochondrial membrane and a compensatory increase in mitochondrial membrane potential with continued respiration, increases both the dye uptake and the retention time in transformed 64F3 cells. These results suggest that mitochondria in FeSV-transformed mink cells may have an abnormally low mitochondrial membrane potential accompanied by a relatively high pH gradient. Since anionic metabolites such as pyruvate and glutamate are accumulated by mitochondria in proportion of the deltapH across the mitochondrial membrane, the abnormal mitochondria described here may contribute to the abnormal metabolic state of FeSV-transformed cells. (Author abstract) (26 Refs)

CELL SURFACE PHENOMENA OF TRANSFORMATION

44. THE SURFACE CHARACTER OF SEPARATED PROSTATIC CELLS AND CULTURED FIBROBLASTS OF PROSTATIC TISSUE AS DETERMINED BY CONCANAVALIN-A HEMADSORPTION.

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Prostate; 2(1):11-21 1981

The surface character of cultured fibroblasts from prostatic tumors by concanavalin A binding was investigated. Normal prostate, benign prostatic hyperplasia (BHP), and prostatic carcinoma (PC) tissues were used. Con A-coated human type O RBC were used for the Con A reactivity assay of separated epithelial cells and cultured fibroblasts. Three PC specimens, six BHP specimens, and one normal prostate were examined for Con A-mediated hemadsorption (HAD) to their epithelial cell surface. All malignant epithelial cells showed higher reactivity than benign epithelial cells. Con A-mediated HAD was highest in permanent cell lines and lowest in benign prostatic epithelial cells, with that of PC cells intermediate between them. Con A reactivity of PC fibroblasts was higher than that of BHP fibroblasts. The use of Con A-mediated HAD is useful for distinguishing malignant epithelial cells of human prostate from nonmalignant cells, although whether the alteration of PC fibroblasts is the cause or the result of carcinogenic transformation of prostatic tissue is unknown. (20 Refs)

45. ADENOVIRUS TYPE 12 T ANTIGEN-RELATED SURFACE ANTIGEN DETECTED BY IMMUNOFLUORESCENCE ON THE MEMBRANE OF TRANSFORMED AND INFECTED CELLS.

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Virology; 117(1):135-145 1982

THA cells, derived from a hamster tumor induced by adenovirus type 12 (Ad12), were analyzed by immunofluorescence for the presence of virus-specific surface antigens. S antigen is a surface antigen detected on suspended living cells by a serum collected from hamsters immunized with Ad12. Besides S antigen, a new surface antigen (surface-T) was observed in formaldehyde-fixed cells treated with anti-T serum. Anti-T serum is not reactive against S antigen in living cells and anti-S serum did not detect surface-T antigen. The membrane location of surface-T antigen was confirmed with a Staphylococcus aureus binding assay. Surface-T antigen seems specific for Ad12, as it is not observed in hamster embryo cells, and is not recognized by antisera against SV40-or polyoma-T antigens nor by antiserum against hamster embryonic antigens. Surface-T antigen is also seen in infected KB cells but not in abortively infected RK13 cells. Anti-P serum, raised against an extract of infected RK13 cells, failed to detect surface-T antigen. Experiments with adsorbed anti-T and anti-S sera confirmed the specificity of surface-T antigen and its distinctiveness from S antigen. (Author abstract) (22 Refs)

46. CELL SURFACE BINDING AFFINITY OF SIMIAN VIRUS 40 T-ANTIGEN.

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Virology; 117(1):173-185 1982

Simian virus 40-transformed cells are characterized by a virus-induced tumor transplantation antigen (SV40 TSTA) defined in vivo by the rejection of tumorigenic SV40-transformed cells in SV40-immunized mice and in vitro by SV40 tumor cell-specific cytotoxic T cells. Several experimental findings support the notion that SV40-infected and -transformed cells express SV40 large tumor antigen (T-Ag) or closely related antigens on the cell surface (surface T). In this report, evidence is presented for a cell surface binding affinity of SV40 T-Ag solubilized and extracted by disruption of SV40-transformed and SV40-infected cells in growth medium. Incubation of various transformed and nontransformed living monolayer cells in situ with these extracts led to a significant uptake of T-Ag to the cell surface (called 'externally bound T-Ag') up to 2-5x higher amounts in comparison to native surface T on SV40-transformed cells. This was demonstrated by the highly sensitive 125I-protein A assay using rabbit antisera directed against purified SV40 T-Ag. Serological analysis of T-Ag in cellular extracts and of externally bound T-Ag revealed no apparent differences suggesting the cell surface binding affinity as a new property of SV40 T-Ag. We interpret our results as an indication that this property enables purified T-Ag to initiate the cellular immune response necessary for the SV40-tumor rejection in mice. (Author abstract) (40 Refs)

47. ALKALINE PHOSPHODIESTERASE I AND ALKALINE PHOSPHATASE I IN PLASMA MEMBRANES OF HERPES SIMPLEX VIRUS TYPE 1 TRANSFORMED HAMSTER CELLS.

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Biochim Biophys Acta; 635(1):94-104 1982

Plasma membrane extracts from Herpes simplex virus Type 1 transformed hamster embryo fibroblasts were chromatographed on Lens culinaris lectin coupled to Sepharose (LcH-Sepharose) and analyzed by dodecyl sulfate polyacrylamide gel electrophoresis. Coomassie blue-staining revealed two major protein bands with apparent mol wt of 125,000 and of about 75,000-90,000. In plasma membranes isolated from these tumor cells prior labeled with [3H]fucose or [3H]glucosamine these bands contained the highest amounts of incorporated radioactivity. Separation by LcH-Sepharose-affinity chromatography as well as metabolic labeling clearly demonstrates their glycoprotein character. The 125,000 protein coincides with alkaline phosphodiesterase I activity with a Km of 6.10(-4) M for TMP p-nitrophenyl ester and is competitively inhibited by UDP-N-acetylglucosamine. This enzymatic activity is also present in normal hamster embryo fibroblasts. Gel electrophoresis of the Lens culinaris lectin-binding glycoproteins from plasma membranes of normal hamster embryo fibroblasts additionally revealed a strong alkaline phosphatase activity represented by an apparent mol wt of 150,000, while HSV1 hamster tumor cells contain only a very weak activity of this enzyme activity. HSV-lytically infected cells, however, have unchanged levels of alkaline phosphatase activity, whereas alkaline phosphodiesterase activity increases slightly. (Author abstract) (36 Refs)

48. CELL SURFACE PROPERTIES OF HLA ANTIGENS ON EPSTEIN-BARR VIRUS-TRANSFORMED CELL LINES.

Smith LM, Petty HR, Parham P, McConnell HM
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Proc Natl Acad Sci USA; 79(2):608-612 1982

A number of monoclonal antibodies have been used to investigate the distributions and rates of lateral motion of the HLA-A,B, and -DR antigens on several Epstein-Barr virus-transformed B-cell lines. The lateral diffusion coefficients (D) of fluorescein conjugates of the monoclonal antibodie s bound to the cell surface were determined by fluorescence recovery after pattern photobleaching. Ds of HLA-A and -B were found to be comparable and of the order of 10(-9) to 10(-10) cm2/sec for each of the seven monoclonal antibodies and four cell lines examined. The HLA antigens appear to be monomeric on the cell surface based on experiments using mixtures of arsanilic acid-conjugated and fluorescein-conjugated antibodies. Four monoclonal antibodies against DR antigens were examined. Two of these, Genox 3.53 and L243, labeled the cell surface uniformly and gave Ds comparable to those obtained for the HLA-A and -B antigens. The other two, DA2 and 2.06, rapidly patched on the cell surface and were immobile. The DA2, L243, and Genox 3.53 antibodies bound outside of the caps formed with the arsanilic acid-conjugated 2.06 antibody and a second-step rhodamine-conjugated rabbit anti-arsanilate antibody. This is consistent with recent biochemical evidence that there are multiple distinct antigens coded for by the HLA-DR region. (Author abstract) (63 Refs)

49. LOSS OF FIBRONECTIN AMONG THE SELECTIVE SURFACE PROTEIN CHANGES ASSOCIATED WITH P-FORMALDEHYDE PROMOTED MEMBRANE VESICULATION.

Rieber M, Rieber MS
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Biochem Biophys Res Commun; 104(2):844-850 1981

Radioiodination followed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis was used to detect proteins in vesicle fractions released when cultured cells were subjected to 25 milli(m)M p-formaldehyde and 2 mM dithiothreitol (DTT). Surface iodination of 'normal' WIRL-3 cells, 'transformed' R72/3 cells, normal rat kidney fibroblasts, and Rat-1 normal fibroblasts revealed upon electrophoresis a major 220 kilodalton (kd) fibronectin-like component. Vesiculation induced by the p-formaldehyde/DTT treatment decreased the component in all but the Rat-1 cells, and increased the lower mol wt fibronectin components, whether iodination took place before or after chemical vesiculation induction. In Rat-1 cells the vesiculation treatment caused a decrease in a surface-associated 140 kd component with an increase in a 130 kd component in the vesicular fraction. The release and selective degradation of cell surface proteins upon chemical vesiculation may involve surface protease activation. (12 Refs)

50. EFFECT OF PH ON FLUORESCENCE POLARIZATION OF DMSO INDUCED FRIEND LEUKEMIC CELLS.

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Cancer Biochem Biophys; 5(3):147-152 1981

Membranes of Friend leukemic cells (FLC) derived from clone 745A of Friend virus transformed cells were studied by diphenyl hexatriene (DPH) fluorescence polarization at pH 4.5, 7.0 and 9.0. Fluorescence polarization values (P) of artificial phosphatidyl choline and phosphatidyl choline/cholesterol liposomes did not change with pH, but when growing FLC and a variant FLC strain (RFLC) resistant to dimethyl sulfoxide (DMSO: 280 milliMoles) induced globin synthesis were analyzed in the same way, P-values increased with pH, but in different ways for different cell lines. The differences were much greater when cells had been treated with DMSO, which induced erythroid differentiation (75% of FLC benzidine dihydrochloride (B) positive on 4th day; less than or equal to 1% of RFLC B+ under same conditions). In both FLC and RFLC, P-value changes related to pH were abolished with 2.5 % glutaraldehyde inhibition of the fluid state of cell membranes and by sodium azide inhibition of the cellular energy generating system. At 4 C, P-values for untreated FLC varied according to pH to the same extent as at 37 C, but DMSO-induced FLC and both untreated and DMSO-treated RFLC exhibited no P-values changes at the lower temperature. P-values could be restored in these cells by raising temperature to 37 C. P-value changes of DPH-labeled FLC reflect lipid-protein interactions; DMSO induction alters these interactions. (28 Refs)

MORPHOLOGICAL AND OTHER BIOLOGICAL ASPECTS OF ONCOGENIC TRANSFORMATION

51. RESTRICTION POINT CONTROL OF CELL GROWTH BY A LABILE PROTEIN: EVIDENCE FOR INCREASED STABILITY IN TRANSFORMED CELLS.

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Proc Natl Acad Sci USA; 79(2):436-440 1982

It has been proposed that animal cells must accumulate a labile protein(s) before they can pass the restriction (R) point in the G1 phase of the cell cycle. Here, we present evidence that this R protein acquires increased stability in transformed 3T3 cells, thereby allowing these cells to continue growth under conditions that arrest untransformed cells. Low doses of cycloheximide or histidinol drastically reduced the rate at which normal 3T3 (A31) fibroblasts in early G1 could enter DNA synthesis. These drugs had less effect on entry of two tumorigenic A31 derivatives, BPA31 and SVA31, into S, although measurement of [3H]leucine incorporation showed that the inhibitors were equally effective in the three cell lines. The hypothesis is that the transformed lines are less sensitive because moderate inhibition of their R protein synthesis is compensated by lower rates of protein degradation. To test this idea, we completely inhibited cytoplasmic protein synthesis for several hours shortly before A31 and BPA31 cells had reached the R point. After removal of inhibitor, A31 cells showed delays in the onset of S that were in excess of the inhibitor pulse, consisted with decay of labile protein during the pulse. BPA31 cells showed no excess delays, suggesting a much more stable R protein. The half-life of the R protein was estimated at 2.5 hr in A31 cells, indicating that, in these cells, R protein synthesis starts at the beginning of G1. In the BPA31 cells the R protein showed no signs of decay for at least 8 hr. (Author abstract) (26 Refs)

52. DO CELL LINES IN VITRO REFLECT THE PROPERTIES OF THE TUMOURS OF ORIGIN? A STUDY OF LINES DERIVED FROM HUMAN MELANOMA XENOGRAFTS.

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Br J Cancer; 44(6):775-786 1981

The characteristics of seven human melanoma cell lines were compared with those of the xenografts from which they were established. The ultrastructure, melanin content, isozyme pattern and chromosome numbers of the cell lines were closely similar to those of the corresponding xenografts. The different cell lines gave rise to colonies in soft agar of size and morphology similar to the parent xenografts, and the plating efficiencies were clearly correlated. However, no correlation was found between the growth rates in vivo and either the doubling times and saturation densities in monolayer cultures or the plating efficiencies in soft agar. Moreover, one of the cell lines lost its tumorigenic ability upon establishment in culture. thus, although the properties of the cell lines by and large reflected those of the parent xenografts, important inconsistencies were seen. The data emphasize that extrapolations from continuous cell lines in vitro to tumor cells in vivo are not necessarily valid. A high content of cellular fibronectin was correlated with a compact colony morphology in soft agar and rapid attachment and spreading on plastic. The growth rates and cellular morphology of the cell lines were strongly influenced by TPA, DMSO, retinoic acid and theophylline, but not by alpha-melanocyte-stimulating hormone. A murine cell line established from one of the xenografts grew in soft agar and produced sarcomas in mice. The malignant murine cells had arisen by transformation of murine stromal cells during the first subcultures in vitro, possibly caused by a factor produced by the human melanoma cells. (Author abstract) (24 Refs)

53. EXPRESSION OF TRANSFORMATION-ASSOCIATED TRAITS IN THE MYOGENIC CELL LINES L6 AND L8.

Bignami M, Dogliotti E, Benigni R, Branca M, Tato F, Alema S
Istituto Superiore di Sanita, Roma, Italy
Exp Cell Res; 137(2):239-248 1982

The presence of cellular alterations, usually associated with transformation, has been studied in two permanent myogenic cell lines, L6 and L8, that retain the ability to differentiate in vitro. We present evidence that, beside being immortal, both cell lines are anchorage-independent for proliferation, a feature not found in primary muscle cells. L6 secretes constitutively high levels of plasminogen activator. L8 is able to undergo multinucleation in the presence of cytochalasin B (cytB) and is tumorigenic in vivo. Single anchorage-independent clones were shown to possess differentiative potentials similar to those of the parental line. Moreover, cell fusion could be directly observed in L8 while still growing as colonies in soft agar. We discuss our data with respect to (i) the reported differences in the regulation of differentiation between primary myogenic cells and continuous cell lines; (ii) the relationship between transformation and differentiation in muscle cells. (Author abstract) (32 Refs)

54. ORIGIN AND BIOLOGICAL PROPERTIES OF A NEW FELINE SARCOMA VIRUS.

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Virology; 117(1):238-244 1982

A new strain of feline sarcoma virus (GR-FeSV) was isolated from a spontaneous sarcoma of an 8-yr-old domestic house cat. The virus induced sarcomas at high incidence after a short latent period in fetal and newborn kittens and transformed cat embryo fibroblasts in vitro after 5 days. Compared to Gardner-Arnstein and the Snyder-Theilen strains of FeSV, GR-FeSV induced more pleomorphic sarcomas and larger, more rounded and discrete foci of cell transformation. GR-FeSV was shown to be defective for replication, and nonproducer transformed clones from several species were obtained at limiting GR-FeSV dilution. The defective sarcoma virus could be rescued from such transformants by superinfection with replication competent type-C viruses. The primary translational product of the GR-FeSV genome is a 70,000-dalton polyprotein that contains the amino-terminal domain of the FeLV gag gene precursor protein and a sarcoma virus-specific polypeptide. These results differentiate GR-FeSV from previously isolated FeSV strains, and establish it as an independent spontaneously occurring sarcoma virus isolate of the domestic cat. (Author abstract) (16 Refs)

ASSAYS OF ONCOGENIC TRANSFORMATION

55. CELL TRANSFORMATION AS A SYSTEM FOR STUDYING MECHANISMS OF CARCINOGENESIS.

Kakunaga T, Crow JD, Lo KY, Hamada H, Kirakawa T

Cell Genetics Section, Lab. Molecular Carcinogenesis, NCI, NIH, Bethesda, MD, 20205

Gann Monogr Cancer Res; 27:231-242 1982

Molecular evidence of mutation occurrence in a chemically-transformed cell is presented. The value and concept of an in vitro mammalian cell transformation system for studying carcinogenesis is discussed. Six subclones of BALB/3T3A31 cells which showed constant susceptibility to induced transformation through more than 50 cell generations were highly susceptible to UV irradiation (A31-1-13), intermediately sensitive (A31-1-1, A31-1-2, and A31-1-7), and resistant (A31-1-8 and A31-1-15). These cell variants were examined for the killing effects of carcinogens, transformation induction by chemical carcinogens, transformation by tumor viruses, induction of ouabain-resistance mutation, and type and amount of DNA adducts formed after treatment with chemical carcinogens and their rate of removal. The results suggest that mutations or DNA damage induced by carcinogens have nothing to do with transformation induction, or that the transformation process involves two steps: the mutational step and a step required for expression of the transformed phenotype. A procedure for isolating a recombinant DNA containing a DNA sequence complementary to a particular messenger RNA for molecular cloning is described. (38 Refs)

56. NEOPLASTIC TRANSFORMATION OF HUMAN DIPLOID FIBROBLASTS TREATED WITH CHEMICAL CARCINOGENS AND CO-60 GAMMA-RAYS.

Namba M, Nishitani K, Fukushima F, Kimoto T, Utsunomiya J, Hayflick L
Dept. Pathology, Kawasaki Medical Sch., Matsushima 577, Kurashiki 701-01, Japan
Gann Monogr Cancer Res; 27:221-230 1982

Transformation of four strains of normal human fibroblasts with repeated treatment with 4-nitroquinoline 1-oxide (4NQO) and two strains with 60Co gamma-rays is reported. Single treatment with those agents had no such effect. A total of 256 experiments were conducted, 116 with 4NQO and 49 with 60Co gamma rays. The transformed cell lines had the following features; epithelial-like morphology, unlimited growth potential, abnormal karyotypes (heteroploid), increased saturation density, reduced growth inhibition by theophylline, increased lactate dehydrogenase isozyme B(H)/A(M) ratio, no large external transformation sensitive protein, elevated colony formation in soft agar, and a low serum requirement for growth. When unlimited growth and abnormal karyotypes are present, neoplastic transformation in human cells is indicated. Criteria of the morphology of transformed colonies were defined. Advantages and disadvantages of using normal human fibroblasts for transformation studies were discussed. Future considerations for the use of normal human fibroblasts for transformation studies were proposed. (21 Refs)

57. SOME ASPECTS OF IN VITRO CARCINOGENESIS USING SYRIAN HAMSTER CELLS.

Umeda M, Enaka K
Tissue Culture Lab., Yokohama City Univ. Sch. Medicine, Urafune-cho 2-33, Minami-ku, Yokohama 232, Japan
Gann Monogr Cancer Res; 27:183-194 1982

Various Syrian hamster cell lots were surveyed in order to establish reliable methods for transformation in culture. Growth of cells which were suitable for transformation experiments was stimulated by treatment with 12-O-tetradecanoylphorbol-13-acetate (TPA). Suitable cells showed low cell density in control cultures and high cell density in TPA-treated cultures. Cells with a capacity for abundant growth were collected by centrifugation on bovine serum albumin discontinuous density gradient. Cells with high multiplication capacity could be collected in fractions at higher density and the cells that sedimented at higher density might be a good source for transformation experiments. Establishment of a cell line likely to have characteristics of contact inhibition of growth, P-TPA cell line, is reported. Of five clones obtained, clone 54 cells exhibited a response of cell growth to TPA stimulation and low cell density in the confluent culture. Clone 54 cells had characteristics similar to those of BALB/3T3 or C3H10T1/2 cells, known to have normal growth characteristics and the capacity to be transformed by carcinogenic stimuli. P-TPA clone 54 cells responded to carcinogens and formed transformed foci. Spontaneous transformation occurred in cells cultured for more than the 20th culture generation. (23 Refs)

58. SISTER CHROMATID EXCHANGES AND MUTAGENIC CARCINOGENS.

Wolff S
Lab. Radiobiology, Univ. California, San Francisco, CA, 94143
Gann Monogr Cancer Res; 27:109-124 1982

Use of sister chromatid exchange (SCE) induction for detecting mutagenic effects in mammalian cells is reported. SCEs are produced with unrepaired lesions are present when the cell passed through S phase and chromosome replicated. Some chemical mutagens caused a 10-fold increase in background level of SCEs at concentrations of the chemical less than 1/100th of that required to induce ordinary chromosomal aberrations. Cultured Chinese hamster ovary cells with rat liver microsomes can be used to detect SCE induction. Suspected mutagens can be prescreened with the SCE test in sensitive mammalian cells by treating the cells in vitro with and without S-9 mix. Negative compounds should be tested in an in vivo test system to determine if the compounds can be activated under in vivo conditions. The SCE test was used to determine the following: which benzene metabolites were most likely responsible for the biologic effects, the stage of embryogenesis at which cells that are genetically capable of producing aryl hydrocarbon hydroxylase activated promutagens or procarcinogens, how long lesions induced by a short-lived proximate carcinogen last in cells of differing repair capacity, and whether mammalian cells exhibit novel DNA repair mechanisms. (58 Refs)

59. CHROMOSOMAL ABERRATION TESTS IN VITRO AS A PRIMARY SCREENING TOOL FOR ENVIRONMENTAL MUTAGENS AND/OR CARCINOGENS.

Ishidate M, Sofuni T, Yoshikawa K
Div. Mutagenesis, Biological Safety Res. Center, Natl. Inst. Hygienic Sciences, Kamiyoga 1-18-1, Setagaya-ku, Tokyo 158, Japan
Gann Monogr Cancer Res; 27:95-108 1982

Approx 500 different compounds were tested for their potential to induce chromosome aberrations in Chinese hamster lung fibroblasts in vitro and/or their mutagenic activity in Salmonella typhimurium in the Ames test. The compounds included 54 carcinogens, 97 food additives, 94 drugs for medical use, 30 pesticides, 46 natural products, and 241 miscellaneous compounds used in laboratories or industry. Overall, approx one-third of the compounds tested were positive in the chromosome test, but not all were positive in the Ames test. Approx 90% and 80% of carcinogens were positive in the chromosome test and Ames test, respectively. Carcinogens not positive in the Ames test were urethan, barbital, ethionamide, diethylstilbestrol, maleic anhydride, and 3-hydroxy anthranilic acid, thiourea, and thioacetamide. Annato, thiram, sodium erythrobate, imipramine-HCl, and vinylidene chloride were positive in the Ames test but not the chromosome test. Chemicals which induce chromosomal aberrations, particularly exchange-type aberrations at low dose levels, can be listed as warning compounds which warrant further testing by in vivo systems to predict their carcinogenic potential and/or genetic hazard in man. (16 Refs)

60. THE USE OF MAMMALIAN CELL MUTANTS TO STUDY THE MECHANISMS OF CARCINOGENESIS.

Trosko JE, Chang CC, Warren ST, Liu PK, Wade MH, Tsushimoto G
Dept. Pediatrics and Human Development, Michigan State Univ., Coll. Human Medicine, East Lansing, MI, 48824
Gann Monogr Cancer Res; 27:159-179 1982

Use of mammalian cell mutants to study the mechanisms of carcinogenesis is reviewed. A genetic approach was used to study molecular mechanisms of initiation and promotion. It was shown that different mutagens induce different types of mutations and that phenotypic expression is influenced by tumor promoters or antipromoters, while mutation fixation is not. General considerations of in vitro mutagenesis at the gene level are discussed. Study of mutagen-sensitive DNA-repair deficient mutants and xeroderma pigmentosum and Bloom's syndrome cells demonstrated that a defect in DNA repair or DNA replication may cause mutagenesis. An in vitro assay to detect tumor promoters was designed with the basic premise that all tumor promoters block metabolic cooperation. Inhibition of cell-cell communication by known tumor promoters might be one of the initial events triggered by tumor promoters. It is possible to study the mechanism of tumor promoters and to screen for environmental promoters. An hypothesis for the relationship of metabolic cooperation and carcinogenesis is proposed. (144 Refs)

GENERAL REVIEWS AND OTHER RELATED STUDIES

61. GENE TRANSFER YIELDS CANCER CLUES.

Marx JL
No affiliation given
Science; 215(4535):955-957 1982

Progress in gene transfer techniques and in identification of transforming genes carried by many of the viruses that cause cancer in animals is reviewed. Studies of onc genes are providing much information about the biochemical basis of viral transformation. Cultured cancer cells derived from human and animal tumors often carry transforming genes that cause normal cells to acquire cancerous characteristics. The applicability of the viral results to the problem of human cancer remains to be investigated. (no Refs)

62. HUMAN CANCERS AND HUMAN VIRUSES.

Waterson AP
Royal Postgraduate Medical Sch., London W12 0HS, England
Br Med J; 284(6314):446-448 1982

The connection between human cancers and human viruses is reviewed. Evidence of malignancies attributable to DNA viruses, similar to those of animals, is growing. A type of human leukemia retrovirus, the human T-cell leukemia virus, has been isolated. Hepatitis B virus has been shown to be of primary hepatocellular carcinoma and Epstein-Barr virus the cause of Burkitt's lymphoma and nasopharyngeal carcinoma; cytomegalovirus may be implicated in Kaposi's sarcoma and human papillomaviruses may cause skin cancer. To be implicated in oncogenesis, a virus should be found in tumor cells and be capable of transforming normal cells of the same species in vitro and inducing tumors in studies with animals. Human T-cell leukemia virus has been shown to be infectious when cultivated with human umbilical cord leukocytes, transforming them into virus-producing lines. Epstein-Barr virus causes disease only rarely on primary infection in childhood, but in adolescence or adult life it gives rise to infectious mononucleosis. Hepatitis caused by hepatitis B virus can be followed by chronic active hepatitis and cirrhosis and is a suspected cause of primary hepatocellular carcinoma. Malignant change has been reported in laryngeal papillomas, in genital warts, and in epidermodysplasia verruciformis. Factors other than viruses which influence malignant transformation are the genetic constitution and immune state of the patient. The virus-cell relation is not simple. (29 Refs)

63. ONCOGENIC VIRUSES AND CELLULAR TRANSFORMATION.

Ruggiero R, Dosne de Pasqualini C
Departamento Leucemia Experimental, Instituto de Investigaciones Hematologicas, Academia Nacional de Medicina, Buenos Aires, Argentina
Bol Acad Nac Med; 59:117-127 1981

Oncogenic viruses (OV) and cellular transformation (CT) were reviewed under the following headings: characteristics of oncogenesis due to virus, types of OV, life cycle of Rous sarcoma virus (RSV), genome of RSV, transformation gene (src), transformation protein (TP) of src gene, and location of action of the phosphoprotein TP with mol wt 60,000. (20 Refs) (In SPA)

64. GENOME INSTABILITY AND CARCINOGENESIS.

Shapot VS, Mironov NM
All-Union Cancer Res. Center, Moscow, USSR
Tsitol Genet; 15(6):73-83 1981

Role of oncogene in neoplastic transformation is reviewed. Presence of oncogene in the cell genome was confirmed in case of transformation induced by DNA-containing viruses and by certain retroviruses. Recent findings that normal cells contain the nonfunctional retrovirus oncogene indicate that the epigenetic changes leading to an expression of 'silent' oncogene are the common causative factors in tumorigenesis. (39 Refs) (In RUS)

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1. AN EVALUATION OF THE GENETIC TOXICITY OF EPICHLORHYDRIN. A REPORT OF AN EXPERT GROUP OF THE INTERNATIONAL COMMISSION FOR PROTECTION AGAINST ENVIRONMENTAL MUTAGENS AND CARCINOGENS.
Sram RJ, Tomatis L, Bridges BA, Clemmesen J
(c/o Lohman), Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(3):299-319 1981

2. ETHYLENE DIBROMIDE (EDB). (REVISED).
NIOSH Document Development Branch
Robert A. Taft Lab., National Inst. Occupational Safety and Health, 4676 Columbia Parkway, Cincinnati, OH, 45226
Curr Intell Bull NIOSH (37): 13 pp., 1981.

3. CHEMICAL CARCINOGENESIS AND SMOKING.
Farber E
Dept. Pathology, Univ. Toronto, Banting Inst., 100 College St., Toronto, Ontario M5G 1L5, Canada
Can J Public Health; 72(6):381-385 1981

RADIATION CARCINOGENESIS

4. CELLULAR TRANSFORMATION BY RADIATION: INDUCTION, PROMOTION, AND INHIBITION.
Borek C
Radiological Res. Lab., Cancer Center/Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 16(4):311-336 1981

5. EFFECTS OF IONIZING RADIATION ON THE DEVELOPING EMBRYO AND FETUS: A REVIEW.
Hoffman DA, Felten RP, Cyr WH
Bureau Radiological Health, Rockville, MD
Effects of Ionizing Radiation on the Developing Embryo and Fetus: A Review. Available from National Technical Information Service, Springfield, VA, as PB82-115379:, 160 pp., 1981.

DIETARY FACTORS IN CARCINOGENESIS

6. BETA-CARBOLINES, PSYCHOACTIVE COMPOUNDS IN THE MAMMALIAN BODY.
Airaksinen MM, Kari I
Dept. Pharmacology, Univ. Kuopio, P.O. Box 138, SF-70101 Kuopio 10, Finland
Med Biol; 59(4):190-211 1981

7. DIET AND CANCER OF THE LARGE BOWEL.
Zaridze DG
Analytical Epidemiology Programme, Div. Epidemiology and Biostatistics, International Agency for Res. on Cancer, 150 Cours Albert Thomas, 69372 Lyon, Cedex 2, France
Nutr Cancer; 2(4):241-249 1981

8. INFLUENCE OF DIET ON MAMMARY CANCER.
Carroll KK
Dept. Biochemistry, Univ. Western Ontario, London, Ontario, N6A 5C1, Canada
Nutr Cancer; 2(4):232-236 1981

9. ARTIFICIAL SWEETENERS IN RELATION TO THE EPIDEMIOLOGY OF BLADDER CANCER.
Howe GR, Burch JD
NCI Canada Epidemiology Unit, Univ. Toronto, Ontario, Canada
Nutr Cancer; 2(4):213-216 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

10. EPIDEMIOLOGY AND THE STUDY OF CANCER.
Woods NF, Woods JS
Dept. Physiological Nursing, Sch. Nursing, Univ. Washington, Seattle, WA
Cancer Nursing. Marino LB, ed. St. Louis, The C. V. Mosby Company, 635 pp., 1981.

11. EPIDEMIOLOGY OF CUTANEOUS MALIGNANT MELANOMA.
Balda BR
Dermatologische Klinik und Poliklinik der Universitat, Frauenlobstr. 9-11, D-8000 Munchen 2, W. Germany
MMW; 123(50):1923-1926 1981
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12. THE SMOKING-INDUCED EPIDEMIC.
Doll R
Green Coll. Oxford, Oxford, England
Can J Public Health; 72(6):372-381 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

13. HEALTH HAZARDS OF ASBESTOS EXPOSURE.
Kaw JL
Industrial Toxicology Res. Centre, Lucknow 226 001, India
J Sci Ind Res; 40(5):342-346 1981

14. OVERVIEW OF FINNISH EPIDEMIOLOGIC STUDIES ON OCCUPATIONAL CANCER.
Tola S
Dept. Epidemiology and Biometry, Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
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15. ALKYLATION OF DNA AND TISSUE SPECIFICITY IN NITROSAMINE CARCINOGENESIS.
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16. TRANSFORMATION INDUCED BY HERPES SIMPLEX VIRUS: A POTENTIALLY NOVEL TYPE OF VIRUS-CELL INTERACTION.
Hampar B
Lab. Molecular Virology, NCI, Frederick, MD, 21701
Adv Cancer Res; 35:27-47 1981

17. ONCOGENESIS BY RNA TUMOR VIRUSES.
Koyama T
Dept. Carcinostasis Res., Tokyo Univ. Medical Res. Inst., 4-6-1 Kindai, Minato-ku, Tokyo 108, Japan
Tanpakushitsu Kakusan Koso; 26(14):2121-2129 1981
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Tumor Virology Lab., Salk Inst., San Diego, CA, 92138
Adv Cancer Res; 35:1-25 1981

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19. EPIDEMIOLOGICAL ASSESSMENT OF DIETARY INTAKE.
James WP, Bingham SA, Cole TJ
Medical Res. Council's Dunn Clinical Nutrition Center, Adenbrooke's Hosp., Cambridge, England
Nutr Cancer; 2(4):203-212 1981

20. ASSESSMENT OF TECHNOLOGIES FOR DETERMINING CANCER RISKS FROM THE ENVIRONMENT.
Office of Technology Assessment
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Assessment of Technologies for Determining Cancer Risks from the Environment. Available from National Technical Information Service, Springfield, VA, as PB81-235400:, 243 pp., 1981.

21. ANTIBODIES SPECIFIC FOR DNA COMPONENTS STRUCTURALLY MODIFIED BY CHEMICAL CARCINOGENS.
Muller R, Rajewsky MF
(c/o Rajewsky) Institut fur Zellbiologie (Tumorforschung), Universitat Essen (GH), Hufelandstrasse 55, Essen 1, W. Germany
J Cancer Res Clin Oncol; 102(2):99-113 1981

22. APPLICATION OF THE MICROBIAL MUTATION TEST IN OCCUPATIONAL HEALTH AND ITS FUTURE PROBLEMS.
Takemura N
Dept. Public Health, Jikei Univ., 25-8, Nishi-Shimbashi 2-chome, Minato-ku, Tokyo, 105, Japan
Sangyo Igaku; 23(4):355-365 1981
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OTHER REVIEWS IN CARCINOGENESIS

23. ARACHIDONIC ACID TRANSFORMATION AND TUMOR PRODUCTION.
Levine L
Dept. Biochemistry, Brandeis Univ., Waltham, MA, 02254
Adv Cancer Res; 35:49-79 1981

24. POLYAMINES IN MAMMALIAN TUMORS PART 1.
Scalabrino G, Ferioli ME
Inst. General Pathology, Univ. Milan, 20133 Milan, Italy
Adv Cancer Res; 35:151-268 1981

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TRANSFORMATION GENE STRUCTURE

1. AMPLIFICATION AND REARRANGEMENT OF ONC GENES IN MAMMALIAN SPECIES.

Chattopadhyay SK, Chang EH, Lander MR, Ellis RW, Scolnick EM, Lowy DR

Dermatology Branch, NCI, NIH, Bethesda, MD, 20205

Nature; 296(5855):361-363 1982

Amplification and rearrangement of transforming (onc) genes was investigated in mammalian species. Sequences related to each onc have been identified in all vertebrate species tested, usual ly one per haploid genome. The rat has at least two different genes homologous to the onc of the rat-derived Harvey murine sarcoma virus (Ha-MuSV). Evidence for the relatively recent amplification of the genes was found by screening genomic DNA from several rodent sequences related to the onc of Ha-MuSV and to the closely related onc of Kirsten (Ki) MuSV. The ras sequences in rodent DNA were studied by electrophoresis and hybridization to a probe derived either from the v-Ha-ras (the onc gene of Ha-MuSV) or v-Ki-ras (the onc gene of Kirsten MuSV). The pattern of c-ras fragments was distinctive for the DNAs from mink, rat, and other Mus species, while the v-Ha-ras probe detected the same c-ras fragments in all M musculus, M castaneus and M poschiavinus. In contrast to the relatively few c-ras fragments in other species, the DNA of a M pahari cell line contained many fragments, representing at least 10 copies per haploid genome. Amplification in M pahari apparently consists of c-Ha-ras sequences; such an occurrence does not seem to be the result of in vitro propagation of the cell line. Genomic DNA from Chinese hamster ovary cells digested with EcoRI contained at least eight fragments which hybridized to the v-Ki-ras probe, while Syrian hamster DNA contained only one such fragment. Possible mechanisms leading to amplification of the ras genes are discussed. (30 Refs)

2. ISOLATION AND CHARACTERIZATION OF A HUMAN LOCUS HOMOLOGOUS TO THE TRANSFORMING GENE (V-FES) OF FELINE SARCOMA VIRUS.

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J Biol Chem; 257(6):2730-2733 1982

A single locus (designated c-fes) in the human genome which exhibits homology to the transformation-specific onc gene (v-fes) of Snyder-Theilen feline sarcoma virus was identified by the Southern blot technique. Recombinant clones containing 16-to 18-kilobase inserts of human DNA including the c-fes locus were constructed. Restriction endonuclease mapping of these clones verified their identity with native human c-fes and demonstrated the presence of at least two sequences in human c-fes interrupting v-fes-homologous regions. The v-fes-homologous locus in the human genome spans about 4 kilobases. The 5'-3' orientation of the c-fes clones with respect to feline sarcoma virus proviral DNA was determined. The region of the human genome that is homologous to v-fes is proximal to the highly reiterated human Alu sequence but not to the highly reiterated human alphoid sequence. (Author abstract) (39 Refs)

3. HUMAN NUCLEOTIDE SEQUENCES RELATED TO THE TRANSFORMING GENE OF A MURINE SARCOMA VIRUS: STUDIES WITH CLONED VIRAL AND CELLULAR DNAS.

Chumakov IM, Zabarovsky ER, Prassolov VS, Mett VL, Kisselev LL
Inst. Molecular Biology, USSR Acad. Sciences, ul. Vavilova 32, Moscow V-334, USS R
Gene; 17(1):19-26 1982

Fragments of the human genome related to onc-gene of Moloney sarcoma virus (MSV), mos-specific, and Moloney leukemia virus (MLV)-specific nucleotide sequences were cloned. An attempt was made to visualize the expression of oncogenes by the Northern blotting technique, using a mos-specific probe, and preliminary data are presented. MSV clone 124 was isolated from tissue culture supernatant obtained from chronically infected TB cells. A total of 3 x 10(5) recombinant phages containing human DNA insert were subjected to screening. [32P]Complimentary (c)DNA-MSV was used as a probe and 30 labeled plaques were obtained. All of them were tested with the mos-specific probe, but with one exception, no mos-specific DNA was detected. After the whole screening procedure, 19 recombinant phages with inserts hybridizable with the mos-specific probe were selected. Clones isolated with various probes could be subdivided into those that contain MLV-related sequences and lack mos-related sequences and those that contain both types of sequences. The hybridization pattern of polyadenylic+RNA from normal mouse liver with [32P]cDNA-MSV is presented. Several fractions were revealed which hybridize also with cDNA-MLV. These RNA appeared to be transcripts of endogenous proretroviruses homologous to MLV which probably are present in mouse liver. When a mos-specific probe was used, no hybridization was detected with RNA isolated independently from several groups of mice. (32 Refs)

4. MOLECULAR CLONING OF DNA FRAGMENTS HOMOLOGOUS TO THE ONCOGEN OF MOUSE SARCOMA VIRUS FROM THE COLLECTION OF GENES OF THE TRANSFORMED CELLS.

Zabarovskii ER, Prasolov VS, Chumakov IM, Kiselev LL
Inst. Molecular Biology, Moscow, USSR
Dokl Akad Nauk SSSR; 261(6):1456-1459 1981

Molecular cloning of murine genes transformed with Moloney sarcoma virus (MSV) showed that sarc-gene is adjacent to the virus-specific nucleotide sequences. Analysis of the collection of molecular clones showed the absence of the provirus DNA identical to MSV genome. The isolated DNA fragments homologous to MSV oncogen were identified as the endogenous defective sarcoma proviruses. (12 Refs) (In RUS)

5. GENETIC STRUCTURE AND TRANSFORMING SEQUENCE OF AVIAN SARCOMA VIRUS UR2.

Wang LH, Hanafusa H, Notter MF, Balduzzi PC
Rockefeller Univ., New York, NY, 10021
J Virol; 41(3):833-841 1982

We have recently shown that a newly isolated avian sarcoma virus, UR2, is defective in replication and contains no sequences homologous to the src gene of Rous sarcoma virus. In this study, we analyzed the genetic structure and transforming sequence of UR2 by oligonucleotide fingerprinting. The sizes of the genomic RNAs of UR2 and its associated helper virus, UR2AV, were determined to be 24S and 35S, respectively, by sucrose gradient sedimentation. The mol wt of the 24S UR2 genomic RNA was estimated to be 1.1 x 10(6), corresponding to 3,300 nucleotides, by gel electrophoresis under the native and denatured conditions. RNase T1 oligonucleotide mapping indicated that UR2 RNA contains seven unique oligonucleotides in the middle of the genome and shares eight 5'- and six 3'-terminal oligonucleotides with UR2AV RNA. From these data, we estimated that UR2 RNA contains a unique sequence of about 1.2 kilobases in the middle of the genome, and contains 1.4 and 0.7 kilobases of sequences shared with UR2AV RNA at the 5' and 3' ends, respectively. Partial sequence analysis of the UR2-specific oligonucleotides by RNase A digestion revealed that there are no homologous counterparts to these oligonucleotides in the RNAs of other avian sarcoma and acute leukemia viruses studied to date. UR2-transformed nonvirus-producing cells contain a single 24S viral RNA which is most likely the message coding for the transforming protein of UR2. On the basis of the uniqueness of the transforming sequence, we concluded that UR2 is a new member of the defective avian sarcoma viruses. (Author abstract) (37 Refs)

6. DNA SEQUENCE HOMOLOGY AND CHROMOSOMAL DELETION AT A SITE OF SV40 DNA INTEGRATION.

Stringer JR
Cold Spring Harbor Lab., Cold Spring Harbor, NY, 11724
Nature; 296(5855):363-366 1982

The possibility that integration of simian virus 40 (SV40) might involve matching of short stretches of homologous sequences present in the otherwise heterologous SV40 and cellular genomes was explored in Fisher rat embryo fibroblasts that were transformed by SV40 infection (SVRE9 cells). A rat DNA fragment (9L) was sequenced and was shown to contain an unoccupied site of SV40 DNA integration. The SVRE9 cells were haploid for their single SV40 insertion. The putative unoccupied integration site was isolated from a library of endo:R:SstI-digested SVRE9 DNA. Analysis of Sst9.1 DNA by restriction endonuclease digestion and blot hybridization localized the SV40 integration site to a 200-base pair endo:R:Sau3a fragment. SV40 DNA and rat DNA shared a 5-base pair sequence homology at a point coincident with the rat-SV40 junction in 9L DNA. The DNA sequence of the unoccupied SV40 integration site was repetitive, containing 12 thymine-guanine (T-G) pairs in tandem and composed almost entirely of T and G. A rearrangement of the rat genome, probably by a deletion of at least 3 kilobases, occurred at the site of SV40 integration. Thus, DNA sequence homology may mediate integrative recombination between SV40 DNA and the cellular chromosome. (25 Refs)

7. STABILITY OF POLYOMA DNA SEQUENCES AND VIRUS-CODED PROTEINS DURING TUMOR FORMATION.

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J Virol; 41(3):1000-1006 1982

To determine the stability of polyoma viral DNA in transformed rat cells during their growth in vivo, we compared the state and arrangement of polyoma virus DNA sequences in virus-transformed rat cell lines before and after their passage in vivo. In cell lines from 12 independent tumors induced by the inoculation of animals with three different transformed cell lines, we could detect no significant changes in the arrangement of viral DNA sequences associated with the in vivo passage of these cell lines. In 13 of 14 tumor cell lines examined, the pattern of polyoma virus tumor antigens, characterized by the presence of the polyoma virus large, middle, and small tumor antigens, was unchanged. (Author abstract) (23 Refs)

8. DELETIONS WITHIN THE TRANSFORMATION-SPECIFIC RNA SEQUENCES OF ACUTE LEUKEMIA VIRUS MC29 GIVE RISE TO PARTIALLY TRANSFORMATION-DEFECTIVE MUTANTS.

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J Virol; 41(3):754-766 1982

The viral RNAs of three nonconditional mutants of avian myelocytomatosis virus MC29 were analyzed. These mutants, which were originally isolated from the quail producer line Q10 and were designated 10A, 10C, and 10H, have lost most of the ability to transform hematopoietic cells in vitro and to induce tumors in vivo, but they still transform cultured fibroblasts with the same efficiency as wild-type (wt) MC29. Electrophoretic analyses showed that the mutant genomic RNAs were smaller than the 5.7-kilobase genome of wt MC29; the genomes of mutants 10A, 10C, and 10H were about 5.5, 5.3, and 5.1 kilobases long, respectively. Analyses of the transformation-specific sequences of these mutant RNAs by a combination of T1 oligonucleotide fingerprinting and hybridization with cDNA from the transformation-specific sequences myc of wt MC29 or competition hybridization including wt MC29 RNA revealed that deletions of myc-specific sequences had occurred. The deletions in all three mutants overlapped, since they all had lost one particular myc-specific oligonucleotide. In agreement with the size of the genomic RNAs, mutants 10C and 10H had lost two additional myc oligonucleotides, and mutant 10A contained a modified myc oligonucleotide. The locations of the deletions were deduced from comparisons with previously established oligonucleotide maps of several members of the MC29 subgroup of acute leukemia viruses and by hybridization of wt and mutant RNAs to molecularly cloned subgenomic fragments of wt MC29 proviral DNA, representing the 5' and 3' domains of the myc sequence. We found that the deleted sequences represented overlapping internal segments of the myc sequence and that the borders of myc with the partial complements of the virion genes gag and env appe ared to be conserved in mutant and wt MC29 RNAs. The correlation between the altered transforming potential for hematopoietic cells and the partial deletion of myc in the mutant RNAs provided direct genetic evidence for the involvement of myc in oncogenesis. However, the unaffected efficiency of these mutants in fibroblast transformation suggested that the deleted sequences are not essential for the fibroblast-transforming potential of the onc gene of MC29. (Author abstract) (31 Refs)

9. MUTATION CAUSING PREMATURE TERMINATION OF THE POLYOMA VIRUS MEDIUM T ANTIGEN BLOCKS CELL TRANSFORMATION.

Templeton D, Eckhart W
Tumor Virology Lab., Salk Inst., San Diego, CA, 92138
J Virol; 41(3):1014-1024 1982

We used site-specific mutagenesis to introduce a termination codon, TGA, into the reading frame for the polyoma virus medium T antigen. We induced this mutation in a region of the polyoma genome in which the overlapping coding regions for the large and medium T antigens are translated in different reading frames. Therefore, the mutation terminated translation of the medium T antigen, but it caused only a single amino acid substitution in the large T antigen and did not affect the small T antigen. Cells infected by the mutant virus produced normal-size small and large T antigens. The infected cells produced a 28,000-dalton fragment of the 48,000-dalton medium T antigen, whose size and tryptic peptide map were consistent with its being a truncated N-terminal fragment terminating at the new termination codon of the mutant. Immunoprecipitates of mutant-infected cell extracts did not show medium-T-antigen-associated protein kinase activity. The mutant virus replicated normally in mouse 3T6 cells and induced cellular DNA synthesis in resting mouse 3T3 cells, but it failed to transform rat or hamster cells, as judged by focus formation and growth in agar. The mutant complemented a tsA mutant which affects the large T antigen for transformation, implying that the mutant defect for transformation was in the medium T antigen. These results imply that the small T antigen and the large T antigen together are insufficient to cause transformation and support the conclusion that the medium T antigen is essential for cell transformation by polyoma virus. (Author abstract) (31 Refs)

10. ISOLATION AND BIOCHEMICAL CHARACTERIZATION OF PARTIALLY TRANSFORMATION-DEFECTIVE MUTANTS OF AVIAN MYELOCYTOMATOSIS VIRUS STRAIN MC29: LOCALIZATION OF THE MUTATION TO THE MYC DOMAIN OF THE 110,000-DALTON GAG-MYC POLYPROTEIN.

Ramsay GM, Hayman MJ
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J Virol; 41(3):745-753 1982

Recently, we isolated three mutants of MC29 virus which, although able to transform fibroblasts with the same efficiency as wild-type MC29, were 100-fold less efficient at transforming macro phages. In this study we found that MC29-transformed quail producer cell line Q10 was able to generate these partially transformation-defective mutants at a high frequency. Using tryptic peptide mapping, we determined that the smaller gag-myc polyproteins encoded by the transformation-defective viruses had lost myc-specific tryptic peptides. This suggested that the mutations which resulted in the transformation-defective viruses being inefficient at transforming macrophages were located in the v-myc sequence and thus directly implicated v-myc and the gag-myc polyprotein in transformation by MC29. (Author abstract) (35 Refs)

11. MOBILITY OF ENDOGENOUS ECOTROPIC MURINE LEUKEMIA VIRAL GENOMES WITHIN MOUSE CHROMOSOMAL DNA AND INTEGRATION OF A MINK CELL FOCUS-FORMING VIRUS-TYPE RECOMBINANT PROVIRUS IN THE GERM LINE.

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Lab. Biochemistry, Univ. Nijmegen, 6525 EZ Nijmegen, The Netherlands
J Virol; 41(3):901-908 1982

Characterization of endogenous ecotropic Akv proviruses in DNA of low and high leukemic mouse strains revealed the presence of one to six copies of the Akv genome per haploid genome equivalent integrated in the germ line. Low leukemic strains analyzed so far contained only one complete copy of the Akv proviral DNA. The site of integration varied among strains, although genetically related strains often carried the Akv proviral gene in the same chromosomal site. The different substrains of the AKR mouse displayed the presence of variable numbers (2 to 6) of Akv genomes. In all substrains one Akv genome was present in an identical chromosomal site; this locus probably comprised the progenitor genome. Closely related substrains had several Akv proviral DNAs integrated in common sites. The accumulation of Akv genomes in the germ line of the AKR/FuRdA strain is likely the result of independent integration events, since backcross studies with the Akv-negative 129 strain showed random segregation of all six proviral loci. The AKR/Cnb strain carried a recombinant provirus in the germ line. This provirus resembled in structure the AKR mink cell focus-forming viruses, which are generated by somatic recombination during leukemogenesis. Therefore, the germ-line amplication of Akv proviral DNAs occurs most likely through infection of embryonic cells by circulating virus. (Author abstract) (28 Refs)

12. ONCOGENES.

Bishop JM
Univ. California, San Francisco, CA
Sci Am; 246(3):80-84,87-92,154 1982

Recent developments in cancer research concerning inducement of cancerous growth are reviewed. Some tumor viruses (TV) are oncogenic only in animals that are not hosts in nature, others are oncogenic only in their natural host. Transformation of cultured cells by TV makes possible the examination of the interaction of a TV with a host cell under controlled conditions, thus avoiding the difficulties associated with experiments in animals. Some viruses have a single gene which can induce tumors, or in some cases, a few such 'oncogenes'. Retroviruses (RV) are the only TV with an RNA genome. The src oncogene of Rous sarcoma virus is discussed. The protein encoded by src is a 60,000 mol wt phosphoprotein. Phosphorylation of tyrosine is a common characteristic of oncogene-encoded enzymes and also has a role in regulating the growth of normal cells. The mutational hypothesis proposes that viral oncogenes differ from their cellular progenitors as a result of mutations introduced when the cellular genes were copied into the RV genome. The dosage hypothesis suggests that RV oncogenes overburden cells with too much essentially normal proteins carrying out normal functions. Excessive activity might tip the balance of regulation toward incessant growth. In tumors induced by the chicken lymphoma viruses, the viral DNA is almost always inserted into cellular DNA in the immediate vicinity of a single cellular oncogene, and the expression of the cellular oncogene is greatly amplified. Gene-length bits of DNA isolated from some tumors can transmit the property of cancerous growth when they are introduced into previously normal cells in culture. (4 Refs)

TRANSFORMATION GENE EXPRESSION AND REGULATION

13. RETROVIRUS LONG TERMINAL REPEATS ACTIVATE EXPRESSION OF CODING SEQUENCES FOR THE HERPES SIMPLEX VIRUS THYMIDINE KINASE GENE.

Joyner A, Yamamoto Y, Bernstein A
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Proc Natl Acad Sci USA; 79(5):1573-1577 1982

In this study, we demonstrate that the long terminal repeats (LTRs) of a murine retrovirus can activate expression of heterologous gene coding sequences from which a functional promoter region has been deleted. Recombinant plasmid clones were obtained that contained both cloned fragments of Friend spleen focus-forming virus (SFFV) DNA and the herpes simplex virus (HSV) thymidine kinase (TK; ATP:thymidine 5'-phosphotransferase, EC 2.7.1.21) gene (tk). The effects of the LTR on tk expression were determined by constructing clones containing tk coding sequences with or without 5' sequences necessary for the initiation of transcription, inserted either 200 or 1,200 base pairs downstream from the SFFV 5' LTR. The expression of the HSV TK protein by these clones was tested by gene transfer of the clones into TK- mouse cells and assay of TK enzyme activity in TK+ transformants. These experiments demonstrate that: (i) the SFFV 5' LTR activates expression of tk coding sequences when these sequences are inserted 200 base pairs downstream from, and in the same orientation as, the LTR; (ii) tk is not activated when placed 1,200 base pairs downstream from, and in the same orientation as, the LTR or when tk is inserted in either site in the opposite orientation as the LTR; (iii) the SFFV 5' LTR does not interfere with in vivo expression of tk when it is flanked by homologous 5' promoter sequences. The implication of these observations for retrovirus oncogenesis and animal cell genetics is discussed. (Author abstract) (40 Refs)

14. EXPRESSION OF HERPESVIRUS THYMIDINE KINASE GENE UNDER CONTROL OF EARLY PROMOTER OF SV40.

Pater MM, Pater A, Di Mayorca G, Smiley JR
Dept. Microbiology, New Jersey Medical Sch., Coll. Medicine and Dentistry New Jersey, 100 Bergen St., Newark, NJ, 07103
Virology; 117(2):536-540 1982

A 0.31-kilobase fragment of SV40 DNA containing the early promoter of this virus was isolated. The pX1 plasmid containing the herpesvirus thymidine kinase gene (TK) was cleaved with BglII and SalI to remove the TK promoter. The SV40 DNA fragment was mixed with the TK gene without its promoter and blunt-end ligated after treatment with S1 nuclease. The newly engineered plasmid was used for the transformation of TK-deficient LtA cells to TK+ phenotype. Blot hybridization experiments show that the plasmid is integrated into high-mol-wt DNA in both of the transformed colonies that we have studied. Also the mRNA in these cells is a hybrid molecule containing both TK and SV40 sequences. (Author abstract) (29 Refs)

15. ADENOVIRUS E1B-58KD TUMOR ANTIGEN AND SV40 LARGE TUMOR ANTIGEN ARE PHYSICALLY ASSOCIATED WITH THE SAME 54 KD CELLULAR PROTEIN IN TRANSFORMED CELLS.

Sarnow P, Ho YS, Williams J, Levine AJ
State Univ. New York, Stony Brook, NY, 11794
Cell; 28(2):387-394 1982

The adenovirus E1b-58kd tumor antigen has been detected in a physical association with a 54 kilodalton cellular protein in adenovirus-transformed mouse cells. Antibody specific for the E1b-58kd protein coimmunoprecipitates a 54 kd protein from transformed, but not from productively infected, cells. Monoclonal antibody specific for the cellular 54 kd protein coimmunoprecipitates the adenovirus E1b-58kd protein from transformed cell extracts. The same or closely related cellular 54 kd protein, associated with the adenovirus E1b-58kd protein, was present in the SV40 large T antigen-54 kd complex previously detected in SV40-transformed mouse cells. The identity of the 54 kd protein is based on the immunological specificities of the anti-54 kd monoclonal antibodies and partial peptide maps of the 54 kd protein associated with the adenovirus and SV40 tumor antigens. The adenovirus E1b-58kd-54 kd complex, like the SV40 large T antigen-54 kd complex, is heterogeneous in size or mass. While all of the cellular 54 kd protein in the adenovirus-transformed cell extract is found in a complex with the E1b-58kd protein, some of the viral 58 kd antigen is detected in a form not associated with the 54 kd protein. The fact that the adenovirus and SV40 tumor antigens, both required for transformation, can be found in physical association with the same cellular protein in a transformed cell is a good indication that these two diverse viral proteins share some common mechanisms or functions. (Author abstract) (43 Refs)

16. MULTIPLE TRANSFORMATION PHENOTYPES AMONG REVERTANTS OF TEMPERATURE-SENSITIVE MUTANTS IN THE TYPE 5 ADENOVIRUS DNA-BINDING PROTEIN.

Carter TH, Nicolas JC, Young CS, Fisher PB
Dept. Biological Sciences, St. John's Univ., Jamaica, NY, 11439
Virology; 117(2):519-521 1982

Seven independently isolated revertants of temperature-sensitive mutants in the 72K protein of Ad5 were tested for the ability to transform rat cells under a variety of conditions. Using the continuous cell line designated CREF, at 36 C the range of transformation phenotypes of the different revertants included a frequency characteristic of WT and also the elevated frequency associated with the parental temperature-sensitive alleles. Transformation frequency did not correlate with other phenotypes, such as plaque size or plaquing efficiency on HeLa cells at 38.5-39 C. Therefore, although it is likely that the 72K protein modulates transformation, it is possible to dissociate genetically this regulatory function of the protein from its replicative function in permissive infection. (Author abstract) (11 Refs)

17. EXPRESSION OF A CLONED ADENOVIRUS GENE IS INHIBITED BY IN VITRO METHYLATION.

Vardimon L, Kressmann A, Cedar H, Maechler M, Doerfler W
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Proc Natl Acad Sci USA; 79(4,part1):1073-1077 1982

In many viral and nonviral eukaryotic systems, an inverse correlation has been observed between the extent of DNA methylation at 5'-C-C-G-G-3' sites and the extent of expression of specific genes as mRNA. The E2a region of adenovirus serotype 2 (Ad2) DNA encodes the Ad2-specific DNA-binding protein required for viral DNA replication. In three lines of Ad2-transformed hamster cells (HE1, HE2, and HE3), multiple copies of the major part of the Ad2 genome persist in an integrated state. Cell lines HE2 and HE3 do not express the DNA-binding protein whereas line HE1 does so. It has been shown that, in cell line HE1, all 5'-C-C-G-G-3' (Hpa II/Msp I) sites in the E2a region remain unmethylated. Conversely, in lines HE2 and HE3 lacking expression of the E2a region all Hpa II sites are methylated. The cloned E2a region of Ad2 DNA, the HindIII A fragment in pBR322, was methylated in vitro by using Hpa II DNA methyltransferase (5'-C-C*G-G-3') or was left unmethylated. In vitro methylation did not break or nick supercoiled circular DNA. Methylated or unmethylated DNA was then microinjected into the nuclei of Xenopus laevis oocytes, and the subsequent synthesis of Ad2-specific RNA was monitored. In vitro-methylated DNA remained in the methylated state for 24 hr on microinjection into nuclei of Xenopus oocytes; unmethylated DNA remained unmethylated. When the injected DNA had been methylated by using Hpa II DNA methyltransferase, Ad2-specific RNA was not synthesized as late as 24 hr after microinjection. Unmethylated DNA was readily expressed into Ad2-specific RNA. As an internal control, unmethylated histone genes (h22 DNA) from sea urchin were microinjected together with methylated E2a DNA from Ad2. Ad2-specific RNA was not found; h22 DNA-specific RNA was readily detected. This finding ruled out nonspecific inhibitory effects in the methylated DNA preparation. It was also shown that transcription of the unmethylated HindIII A fragment of Ad2 DNA in Xenopus oocytes was initiated on the late promoter of the E2a region. The same promoter was used in productively infected KB cells. Methylation by BsuRI methylase (5'-G-G-C*C-3') did not inactivate the HindIII A fragment. These results provide evidence for the notion that methylated sequences at highly specific sites are involved in the regulation of gene expression. The actual nature of the regulatory signal is not yet understood. (Author abstract) (50 Refs)

18. DIFFERENT MRNAS FROM THE TRANSFORMING REGION OF HIGHLY ONCOGENIC AND NON-ONCOGENIC HUMAN ADENOVIRUSES.

Virtanen A, Pettersson U, Le Moullec JM, Tiollais P, Perricaudet M
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Nature; 295(5851):705-707 1982

Messenger RNA (mRNA) produced from the transforming region of DNA from human adenoviruses was characterized. Adenoviruses were cultured by infection of A549 cells derived from human oat-cell carcinoma. RNA was labeled with 32P. Complementary DNA (cDNA) was prepared from viral mRNA and hybridized to restriction enzyme fragments of viral DNA. The transforming region of viral DNA was characterized by inserting cDNA into pBR322 plasmids and hybridizing to labeled DNA fragments. Characterization of 38 clones containing sequences from the E1B region of the highly oncogenic Ad12 adenovirus showed three classes of mRNA. Ad12 mRNA were compared with mRNA from weakly (Ad5 and Ad7) and non-oncogenic (Ad2) adenoviruses. Results identified two donor sites, designated D1 and D2, and three acceptor sites, designated A1, A2, and A3, in the three classes of mRNA. Donor site D1 was well-conserved and generated a large splice in Ad12 and Ad5. Site D2 was well-conserved and generated a small splice in Ad5, Ad7, and Ad12. Site A1 generated a middle splice in Ad12 not found in Ad5. Site A2 was found in all three viral serotypes. Site A3 was found only in Ad7 and Ad12. Results indicate that mRNA from Ad12 have different structures from mRNA from Ad2, but suggest that the adenoviruses have evolved together. (30 Refs)

19. ANALYSIS OF THE SEQUENCE OF AMINO ACIDS SURROUNDING SITES OF TYROSINE PHOSPHORYLATION.

Patschinsky T, Hunter T, Esch FS, Cooper JA, Sefton BM
Tumor Virology Lab., Salk Inst., P. O. Box 85800, San Diego, CA, 92138
Proc Natl Acad Sci USA; 79(4,part1):973-977 1982

We have identified the single phosphorylated tyrosine in p60src, the transforming protein of Rous sarcoma virus, as part of the sequence NH2-Arg-Leu-Ile-Glu-Asp-Asn-Glu-Tyr(P)-Thr-Ala-Arg COOH. Therefore, this is a sequence that is recognized efficiently by a tyrosine protein kinase in vivo. Phosphorylation of tyrosine in cellular proteins appears to play a role in malignant transformation by four classes of genetically distinct RNA tumor viruses. Phosphorylated tyrosines in several other proteins resemble the tyrosine in p60src in that they are located 7 residues to the COOH-terminal side of a basic amino acid and either 4 residues to the COOH-terminal side of, or in close proximity to, a glutamic acid residue. Therefore, it is possible that these features play a role in the selection of sites of phosphorylation by some tyrosine protein kinases. However, several clear exceptions to this rule exist. (Author abstract) (38 Refs)

20. NUCLEAR LOCALIZATION AND DNA BINDING OF THE TRANSFORMING GENE PRODUCT OF AVIAN MYELOCYTOMATOSIS VIRUS.

Donner P, Greiser-Wilke I, Moelling K
Max-Planck-Institut fur Molekulare Genetik, Berlin-Dahlem, Ihnestrasse 63-73, 1 Berlin 33, W. Germany
Nature; 296(5854):262-266 1982

A previous study has shown that the activated cellular gene in certain lymphomas was homologous to the oncogene of an acute avian leukemia virus, MC29. In MC29, the oncogene is fused to the viral structural gene, gag. The mol wt of the fused gene is 110,000 (110 K) and is designated as p110gag-myc. For further analysis, the 110 K protein was purified from the 35S-methionine-labeled MC29-transformed quail embryo fibroblast cell line MC29-Q8-NP (which does not produce virus particles, but expresses the transforming protein gag-myc) by an immune affinity column containing protein A-Sepharose to which monoclonal anti-p19 IgG was covalently coupled in conditions which link the constant region of the IgG molecule to the solid phase. Immunofluorescence studies and cell fractionation of MC29-transformed fibroblasts indicate that the 110 K protein is predominantly located in the nucleus. The purified protein was found to bind to double-stranded DNA. These properties may be related to the role of the protein in transformation. (22 Refs)

21. EXPRESSION OF THE PRC II AVIAN SARCOMA VIRUS GENOME.

Adkins B, Hunter T, Beemon K
Institut fur Virusforschung, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany
J Virol; 41(3):767-780 1982

We found that the genomic RNA of the replication-defective avian sarcoma virus P RC II was 4.0 kilobases long. A Northern blot analysis of the viral RNAs present in PRC II-transformed cells showed that the PRC II genome was expressed as a single 4.0 kilobase mRNA species. In vitro translation of poly-adenylic acid-containing 70S virion RNA yielded two highly related proteins of 110,000 and 105,000 daltons (P110 and P105), which were synthesized from messenger activity that sedimented as expected for the 4.0 kilobase PRC II genome (at 25 to 27S). P110 and P105 were identified as in vitro translation products of the PRC II genome by immunoprecipitation and tryptic peptide mapping and were the only PRC II-specific polypeptides detected by in vitro synthesis. In addition, we found that immune complexes prepared from PRC II 70S virion RNA in vitro translation products contained a tyrosine-specific protein kinase activity. A comparison of the in vitro- and in vivo-synthesized proteins revealed that PRC II-transformed cells also contained 110,000- and 105,000-dalton proteins, which were indistinguishable from in vitro-synthesized P110 and P105 by electrophoretic mobility and tryptic peptide analysis. Both P110 and P105 were present in producer cells and in seven individual nonproducer clones. A pulse-chase analysis showed that P105 was the primary translation product of the PRC II genome and that P110 was derived from P105 by post-translational modification. Under conditions of long-term labeling with [35S]methionine, P110 and P105 were present in a molar ratio of approximately 1:1. These results indicated that the transformation-specific product of the PRC II genome, previously referred to as a single component (P105), actually consists of two polypeptides related by post-translational modification. (Author abstract) (36 Refs)

22. PHOSPHORYLATION AND METABOLISM OF THE TRANSFORMING PROTEIN OF ROUS SARCOMA VIRUS.

Sefton BM, Patschinsky T, Berdot C, Hunter T, Elliott T
Tumor Virology Lab., Salk Inst., San Diego, CA, 92138
J Virol; 41(3):813-820 1982

The transforming protein of Rous sarcoma virus, p60src, was found to contain 0.5 to 0.9 mol of total phosphate per mol of polypeptide. The protein is known to be phosphorylated at two sites, a serine in the amino-terminal domain and a tyrosine in the carboxy-terminal domain. Because our indirect analysis suggests that the serine is phosphorylated to approx twice the extent of the tyrosine, we estimate that p60src contains approx 0.3 to 0.6 mol of phosphoserine and 0.2 to 0.3 mol of phosphotyrosine per mol of polypeptide. p60src was found to represent approx 0.02% of the total incorporated radioactivity in Rous sarcoma virus-transformed chick cells labeled with [35S]methionine for 48 hr. This corresponds to approx 500,000 molecules of p60src per cell. Pulse-chase experiments revealed that the half-life of p60src ranged from 2 to 7 hr, depending on the strain of virus examined. The p60src of the Schmidt-Ruppin strain was significantly more stable than that of the Prague strain. (Author abstract) (25 Refs)

23. INDUCTION OF FIBROSARCOMA BY RAT SARCOMA VIRUS.

Rasheed S, Young HA
Dept. Pathology, Univ. Southern California Sch. Medicine, 1840 North Soto St., Los Angeles, CA, 90032
Virology; 118(1):219-224 1982

The rat sarcoma virus (RaSV) causes rapid transformation of rat embryo fibroblasts in vitro and induces a 29,000-dalton protein (pp29) in the transformed cells. Several strains of newborn rats were inoculated with RaSV with its natural helper rat leukemia virus (RaLV) or RaSV pseudotypes of replication competent murine leukemia virus or baboon endogenous virus. Approx 2-3% of susceptible rats developed fibrosarcomas in 12-20 wk. However, none showed any immune response or viremia over a 10-mo follow-up period. Further, we isolated RaSV from the in vivo induced tumors that transformed rat cells in vitro. Both the tumor and in vitro transformed cells exhibited the same gene product (pp29) as described earlier. (Author abstract) (17 Refs)

24. CHARACTERIZATION OF A POLYPEPTIDE PRESENT IN HERPES SIMPLEX VIRUS TYPE 2-TRANSFORMED AND -INFECTED HAMSTER EMBRYO CELLS.

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J Virol; 41(3):1095-1098 1982

Transformation of hamster embryo cells by herpes simplex virus stimulated the production of a 35-kilodalton (35K) protein that was specifically immunoprecipitated, along with other polypeptides, by rabbit hyperimmune serum. This 35K polypeptide was further analyzed by partial digestion with Staphylococcus aureus V8 protease in parallel with a 35K polypeptide from herpes simplex virus Type 2-infected cells. These polypeptides had almost identical partial-proteolytic cleavage maps, indicating that they are probably the same or that they are very similar polypeptides. (Author abstract) (25 Refs)

GENETIC AND OTHER HOST FACTORS WHICH MODULATE ONCOGENIC TRANSFORMATION

25. AN AGE-DEPENDENT STOCHASTIC MODEL FOR CARCINOGENESIS.

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Dept. Mathematics, Indian Inst. Technology, Madras 600036, India
Math Biosci; 57(3/4):155-174 1981

An age-dependent 2-stage mathematical model for carcinogenesis is presented. It is assumed that a normal cell can give rise to a neoplasm only after two changes of mutations, the first of which gives rise to an 'intermediate' cell. It is also assumed that both normal and intermediate cells produce clones by stochastic birth and death processes, and that the probability of transition is age-dependent. A similar model has been proposed for retinoblastoma: the hereditary form being a one-mutation model (the first mutation having occurred in an ancestor's germ cell, all retinal cells are intermediate at birth), and the sporadic form being a two-mutation model (both mutations occurring in somatic cells). (21 Refs)

26. RELATIONSHIP BETWEEN THE GENETICALLY DETERMINED ACETYLATOR PHENOTYPE AND DNA DAMAGE INDUCED BY HYDRALAZINE AND 2-AMINOFLUORENE IN CULTURED RABBIT HEPATOCYTES.

McQueen CA, Maslansky CJ, Glowinski IB, Crescenzi SB, Weber WW, Williams GM
Div. Pathology and Toxicology, American Health Foundation, Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Proc Natl Acad Sci USA; 79(4,part1):1269-1272 1982

The relationship between acetylation rates of rabbit hepatocytes and their susceptibility to genotoxicity by DNA-damaging chemicals that undergo N-acetylation was studied in primary cultures of hepatocytes from New Zealand White rabbits that have a genetically determined difference in acetylation rates. Hepatocytes from rapid and slow acetylator rabbits maintained in culture the difference in acetylation rates that existed in vivo. DNA repair, an index of DNA damage, was produced by hydralazine in hepatocytes from slow acetylator rabbits but not in those from rapid acetylators. In contrast to these results, hepatocytes from rapid acetylators were more sensitive than those from slow acetylators to toxicity from the carcinogen 2-aminofluorene and displayed greater amounts of DNA repair. The amount of DNA repair measured with either chemical was dose dependent. These phenotype-dependent differences in the genotoxicity of two DNA-damaging chemicals provide evidence for the role of the acetylation polymorphism as a factor in determining susceptibility to toxicity, and perhaps carcinogenicity, of these chemicals. (Author abstract) (48 Refs)

EXPERIMENTAL MODULATION OF ONCOGENIC TRANSFORMATION

27. SOMATIC MUTATION AND NEOPLASTIC TRANSFORMATION INDUCED BY [METHYL-(3)]THYMIDINE.

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Radiat Res; 90(1):142-154 1982

Effects of tritiated thymidine (3H-TdR) on neoplastic transformation and somatic mutation in Golden Syrian hamster embryo (GSHE) fibroblast cultures were studied and compared with those in cultures treated with tritiated uridine (3H-UdR). Normal GSHE cells were exposed to 3H-TdR for 17 hr, then grown briefly in deoxycytidine- and thymidine-containing medium. A multihit mechanism for reduction of colony formation was suggested, with a Dq value of 0.01 uCi/ml and a D0 value of 0.04 uCi/millimole. Mutagenicity of 3H-TdR was examined with a tumor line, BP6T, established from benzo(a)pyrene-treated GSHE cultures. Mutagenicity was studied at loci coding for hypoxanthine phosphoribosyltransferase (HPRT) and for the Na+/K+ ATPase. A linear dose-response curve was obtained for mutation at the HPRT locus. 3H-TdR incorporation over the concentration range of 0-0.04 uCi/ml corresponded to a biologically effective dose of 0-271 rad. An effective dose of 0.10 rad/decay and a total dose of 2,831 decays were calculated. Over the same tritium dose range, 5-3H-UdR did not induce HPRT- mutations. No mutations to ouabain resistance were observed in any experiments. All cultures treated with 0.04 uCi/ml 3H-TdR became tumorigenic, while control cultures did not. Neoplastic transformation began with morphological alteration, followed by enhanced fibrinolytic activity and the ability to clone in medium containing 1% serum or soft agar. DNA damage caused by 3H-TdR was manifested by induction of somatic mutation, most likely of a frameshift/deletion nature. The findings support the conclusion that DNA damage alone is sufficient to initiate neoplastic transformation. (32 Refs)

28. 5-AZACYTIDINE-INDUCED REACTIVATION OF A HERPES SIMPLEX THYMIDINE KINASE GENE.

Clough DW, Kunkel LM, Davidson RL

Center for Genetics, Univ. Illinois Medical Center, 808 South Wood St., Chicago, IL, 60612

Science; 216(4541):70-73 1982

Mouse cells transformed with herpes simplex virus and containing the viral thymidine kinase (TK) gene in an inactive state were treated with 5-azacytidine. The result was the reexpression of the viral TK gene. Two days of exposure to 5-azacytidine followed by 2 days of expression time was sufficient for maximal induction of the TK+ phenotype. The induction of TK expression by 5-azacytidine was concentration-dependent, with maximal induction at 10 micromoles per liter. 5-Azacytidine also inhibited the decay of TK expression in TK+ transformants removed from selective conditions. Analysis of the methylation patterns of the viral TK gene with restriction endonucleases Hpa II and Msp I showed the active gene to be unmethylated, the inactive gene methylated, and the 5-azacytidine-induced gene unmethylated. (Author abstract) (18 Refs)

29. EFFECT OF BENZALDEHYDE ON A MALIGNANT PHENOTYPE OF TRANSFORMED RAT LIVER CELLS.

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Agric Biol Chem; 45(12):2815-2821 1981

Effects of benzaldehyde (BA) on malignant phenotype were studied in transformed rat liver cells. Culb TC/R/TC cells were produced by in vitro transformation of rat liver cells with 4-nitroquinoline-1-oxide, back transplantation into rats, and re-cultured. Cultures were exposed to 1 x 10(-3) M or 2 x 10(-3) M BA. Untreated control cultures showed rapid proliferation for four days, followed by slower proliferation through day 14. Growth of control cells indicated that Culb TC/R/TC cells are capable of unlimited growth without contact inhibition of cell division. Cultures exposed to 1 x 10(-3) M BA showed a growth curve almost parallel, but slightly lower than the growth curve for controls. The inhibition ratio at the lower BA concentration was 2% in the initial stage, increasing to 50% between days 8-12 and decreasing to 40% at day 14. At the higher concentration of BA proliferation was reduced by 30% compared with controls at day 2 and by 60% at day4; no growth was noted after day 4. Removal of medium containing BA and addition of BA-free medium was followed by renewed growth of cultures, indicating that the effect of BA was reversible. Control cells exhibited 'piled-up' growth. BA inhibited this type of growth, cultures being monolayer. Results suggest that BA restores functions of normal cells, including cell constant inhibition, in malignant cells. (13 Refs)

30. RETINOIC ACID INDUCES ANCHORAGE- AND DENSITY-DEPENDENT GROWTH WITHOUT RESTORING NORMAL CYTOSKELETON, EGF BINDING, FIBRONECTIN CONTENT AND ODC ACTIVITY IN A RETROVIRUS-TRANSFORMED MOUSE CELL LINE.

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Exp Cell Res; 138(1):95-107 1982

We studied the effects of retinoic acid (RA), a known tumor inhibitor, on a group of transformation-related properties expressed by a Kirsten sarcoma virus (Ki-MSV)-transformed BALB/c 3T3 (clone A31) cell line (KA31). The aim was to determine whether any one or a group of such transformation-specific changes, exhibited by this cell line, is an absolute prerequisite for its acquisition of the neoplastic state. Our study shows that RA treatment restores two important parameters of normalcy in KA31 cells: density-dependent growth inhibition, and anchorage-dependent growth. Retinoic acid also induces cell-to-substratum adhesiveness in a significant proportion of the treated KA31 cell population. However, four other markers of transformation - loss of microfilaments, lack of surface fibronectin, reduced epidermal growth factor (EGF) binding, and increased ornithine decarboxylase activity - remain unaltered by RA treatment. These transformation-specific changes, therefore, are dissociable from loss of anchorage- and density-dependent growth. It is suggested that RA may intervene in transforming protein kinase-induced cell surface changes that are involved in cellular malignancy and the loss of growth control in KA31 cells. (Author abstract) (57 Refs)

31. CYCLIC NUCLEOTIDE MODULATION OF IN VITRO MORPHOLOGICAL TRANSFORMATION OF SYRIAN HAMSTER CELLS.

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Dept. Pathology, Univ. South Carolina Sch. Medicine, Columbia, SC, 29208
Cancer Res; 42(4):1274-1278 1982

The cyclic nucleotides, cyclic adenosine 3':5'-monophosphate (cAMP) and cyclic guanosine 3':5'-monophosphate (cGMP) or their dibutyryl and monobrominated derivatives, may either increase or decrease morphological transformation of Syrian hamster embryo cells exposed to N-methyl-N'-nitro-N'-nitrosoguanidine (MNNG). The effect on transformation is primarily a function of the parent cyclic nucleotide and the duration of exposure to the nucleotides. At concentrations of 5 mM or larger for a minimum 24-hr exposure cAMP, cGMP, and their congeners reduced the colony-forming ability of nontransformed Syrian hamster embryo cells not exposed to MNNG; however, cGMP and its derivatives caused less toxicity than cAMP or its analogs. cAMP and its monobrominated and dibutyrylated derivatives decreased the transformation frequency associated with MNNG irrespective of whether the various adenylnucleotides were administered before or after MNNG. The greatest inhibitory effect on MNNG-induced transformation was obtained with N6,O2-dibutyryl cyclic adenosine 3':5'-monophosphate followed in order by 8-bromocyclic adenosine 3':5'-monophosphate and cAMP. At equimolar doses, the dibutyryl and brominated analogs of cGMP but not unsubstituted cGMP enhanced transformation when administered prior to exposure of the Syrian hamster embryo cells to MNNG but reduced the transformation frequency when added after MNNG. The enhancing and inhibitory effects of the guanine cyclic nucleotide-induced alteration of MNNG-associated transformation frequencies were dose and time dependent and occurred in the order N6,O2-dibutyryl cyclic guanosine 3':5'-monophosphate greater than 8-bromocyclic guanosine 3':5'-monophosphate very much greater than cGMP. Butyric acid neither diminished nor increased MNNG-induced transformation frequency. The latter suggests that butyrate ions formed by metabolism of the cyclic nucleotide analogs were not a factor in the observed alterations of transformation frequency. (Author abstract) (35 Refs)

32. MOUSE EMBRYOS CONTAIN POLYPEPTIDE GROWTH FACTOR(S) CAPABLE OF INDUCING A REVERSIBLE NEOPLASTIC PHENOTYPE IN NONTRANSFORMED CELLS IN CULTURE.

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Section Experimental Pathology, Dept. Cell Biology, Mavo Clinic/ Foundation, Rochester, MN, 55905
J Cell Physiol; 110(2):169-174 1982

Seventeen-day Swiss albino mouse embryos were subjected to an acid/ethanol extraction which has been used to isolate transforming-growth factors (TGF) from tumors. After dialysis against 1% acetic acid, the extract was lyophilized and clarified. Various concentrations were tested for their ability to stimulate AKR-2B mouse cells to form colonies in soft agar. The extract was effective at concentrations greater than 10 ug/ml. A correlation between protein concentration and enhancement of the size and number of colonies formed was apparent. When fractionated on a Bio-Gel P-60 column, the major peak of colony-stimulating activity (CSA) was in the 15,000 mol wt range. A smaller peak of CSA was observed in the 22,000 mol wt range with the higher concentration of the fractions. Late eluting epidermal growth factor (EGF) activity was observed which probably represents embryonal EGF. Pooled material containing the major peak of CSA produced a 50% level of CSA in the 100 ug range similar to the effect of TGF on transformed AKR cells. At a level of 1 mg/ml, the pooled material caused 50% competition of 125I-EGF binding to A431 human squamous cell carcinoma clone cell EGF receptors, which is also comparable to the activity of TGF from transformed AKR cells. The substance, designated as mouse embryo factor (MEF) caused AKR-2B cells to assume a transformed phenotype identical to that of the chemically transformed AKR cells. Effects of heat indicated that, like TGF, the biological activity of MEF is due to a polypeptide with disulfide bonds. Further separation revealed two peaks of soft agar dermal growth factor receptor-competing activity. The similarities of MEF to previously identified transforming growth factors suggest that both fetal development and neoplastic transformation may be affected by similar mechanisms. (15 Refs)

33. EFFECT OF MAGNESIUM CONTENT ON DENSITY-DEPENDENT REGULATION OF THE ONSET OF DNA SYNTHESIS IN TRANSFORMED 3T3 CELLS.

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Cancer Res; 42(5):1761-1768 1982

A spontaneously transformed clone of BALB/c 3T3 cells became more transformed after more than 90 passages as indicated by increased rounding of cells, multiplication to a higher saturation density, and increased ability to form colonies when suspended in agar. When the extracellular concentration of Mg++ was sharply reduced, the highly transformed cells flattened, assumed the shape of nontransformed cells, and became regularly arranged in cohesive arrays. If crowded when deprived of Mg++, they lost more intracellular Mg++ than did nontransformed and early passage-transformed cells and remained at constant cell density for at least 10 days. The intracellular content of neither Na+ nor K+ changed consistently, with Mg++ deprivation, but the Ca++ content increased more than two-fold. The sensitivity of the onset of DNA synthesis to inhibition by Mg++ deprivation increased with the extent of crowding of the cultures. This was demonstrated by varying population density within a single culture dish as well as from culture to culture. The loss of intracellular Mg++ in low concentrations of extracellular Mg++ increased with cell crowding as did the inhibition of DNA synthesis per fractional loss of intracellular Mg++. Neither deprivation of K+ or Ca++ nor addition of cyclic adenosine 3':5'-monophosphate produced a density-dependent inhibition of DNA synthesis. The results indicate that a reduction of the Mg++ content of highly transformed cells restores density-dependent inhibition of the onset of DNA synthesis, which is a character istic property of nontransformed cells. The differences in Mg++ retentiveness with population density may reflect differences of intracellular distribution and binding of Mg+, which could in turn explain some of the regulatory effects of population density on metabolism and growth. (Author abstract) (16 Refs)

34. GENETICAL MECHANISMS OF CARCINOGENESIS. THE 'ONCOGENETICS' PROGRAM.

Shapiro NI
No affiliation given
Vestn Akad Nauk SSSR; (12):69-75 1981

Current research in the field of somatic cell genetics is reviewed. Applications of the somatic cell genetics methods to the study of the mechanisms of virus carcinogenesis showed that simian virus 40 (SV40) and adenovirus Type 3 induced gene mutation in chinese hamster cells. The mutagenic effect of DNA-containing oncogenic viruses was not locus-specific. Both mutagenesis and neoplastic transformation of cells were mediated via the same mechanism of incorporation of SV40 genome into genome of mammalian cells. (no Refs) (In RUS)

BIOCHEMICAL AND MOLECULAR BIOLOGICAL STUDIES OF TRANSFORMED PHENOTYPE

35. CORRELATION BETWEEN THE RATES OF AEROBIC GLYCOLYSIS AND GLUCOSE TRANSPORT, UNRELATED TO NEOPLASTIC TRANSFORMATION, IN A SERIES OF BALB 3T3-DERIVED CELL LINES.

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Lab. Biochemistry, NCI, NIH, Bethesda, MD, 20205
Cancer Res; 42(5):1809-1816 1982

The relationship between transformation, lactate production, and glucose transport was examined in a series of 10 cell lines consisting of subclones of BALB 3T3 A31 cells and viral and chemical transformants of either the subclones or the original A31 line. Comparisons were made over a relatively narrow range of cell densities to minimize changes in the biochemical parameter during growth. A nitroquinoline oxide (NQT-3T3-714) and a temperature-sensitive Kirsten sarcoma virus (tsKi-3T3-714) transformant of subclone 714 exhibited transformed phenotypes with respect to morphology and growth properties, but their rates of lactate production and 2-[3H]deoxy-D-glucose (deoxyglucose) uptake were similar to those of the parent cells. Inhibitors of oxidative phosphorylation increased glycolysis fold in these transformants, showing that there was no defect in the enzymes of this pathway. At a temperature non-permissive for transformation of tsKi-3T3-714, lactate production by this line did not decrease relative to the rate of the parent cells. Another transformant, Ki-3T3-234, had a glycolytic rate which was 4 to 5x greater than that of the low lactate producers while other transformants exhibited intermediate rates, and the rate of a third nontransformed 3T3 A31 subclone, K-1-1, was comparable to the rate of Ki-3T3-234. The rates of [3H]deoxyglucose uptake by this series of cells were closely proportional to their glycolytic rates rather than to their state of transformation. Increasing glycolysis by oligomycin or dinitrophenol treatment, however, did not cause a concomitant increase in sugar uptake. Neither glycolysis nor deoxyglucose uptake in the high-lactate producer (Ki-3T3-234) was inhibited by ouabain, suggesting that Na+-K+ adenosinetriphosphatase is not a regulator of these functions in 3T3 cells. In 3T3-derived cells, it appears that the rates of glycolysis and glucose uptake may be regulated in tandem under some conditions and that neither process is an obligatory consequence of neoplastic transformation. (Author abstract) (31 Refs)

36. DECREASE IN PROTEIN CONTENT AND CELL VOLUME OF CULTURED DOG KIDNEY EPITHELIAL CELLS DURING GROWTH. IMPORTANCE FOR TRANSPORT MEASUREMENTS.

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In Vitro; 18(3):196-202 1982

Protein content per cell and cell volume of the canine kidney epithelial cell line, MDCK, and one of its chemically induced tumorigenic transformants (T1) were examined during growth in serum-containing and serum-free, hormonally defined media. Both protein content per cell and cell volume (measured with 3-O-methyl-D-glucose) decreased when cell density increased. Significant inverse linear correlations were found between protein content (and cell volume) and the log of the cell number. Equations relating these variables were derived. No difference was detected between cells grown in serum-containing and in serum-free media. Results of 22Na+ uptake experiments differed markedly when expressed as a function of cell number or as a function of protein content or cell volume. However, protein content and cell volume bore a constant relationship to one another, and expression of results as a function of protein content or cell volume yielded qualitatively similar results. These findings show that in MDCK cells, as in other cell lines, protein content and cell volume decrease markedly during growth and that these variations must be taken into account when expressing and interpreting the results of transport measurements. (Author abstract) (25 Refs)

37. PROTEINS ANTIGENICALLY RELATED TO THE HUMAN ERYTHROCYTE GLUCOSE TRANSPORTER IN NORMAL AND ROUS SARCOMA VIRUS-TRANSFORMED CHICKEN EMBRYO FIBROBLASTS.

Salter DW, Baldwin SA, Lienhard GE, Weber MJ
Dept. Microbiology and Public Health, Michigan State Univ., East Lansing, MI, 48823
Proc Natl Acad Sci USA; 79(5):1540-1544 1982

Antibody raised against the purified human erythrocyte glucose transporter specifically precipitated four proteins from normal and Rous sarcoma virus-transformed chicken embryo cells: a major protein of Mr 41,000 and minor proteins of Mr 68,000, 73,000, and 82,000. The Mr 41,000 and 82,000 proteins were found only in a membrane fraction, not in the soluble fraction, and displayed a heterogeneous mobility on NaDodSO4/polyacrylamide gel electrophoresis, suggesting glycosylation. The Mr 41,000 and 82,000 proteins were increased in amount after malignant transformation in direct proportion to the increase in hexose transport rate, and the increase was dependent on the expression of the src gene product, as revealed with a temperature-conditional src mutant. We suggest that the Mr 41,000 and 82,000 proteins are the glucose transporter of chicken embryo fibroblasts, or a component of the glucose transporter. These experiments provide direct evidence that malignant transformation increases the rate of glucose transport by increasing the number of transporters in the membrane. (Author abstract) (27 Refs)

38. DNA METHYLATION LEVELS IN NORMAL AND CHEMICALLY-TRANSFORMED MOUSE 3T3 CELLS.

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Biochem Biophys Res Commun; 104(4):1489-1494 1982

Normal mouse embryo 3T3 cells grown in culture and cells transformed by benzo(a)pyrene and methylcholanthrene were analyzed by high performance liquid chromatography (HPLC) to determine the 5-methylcytosine to cytosine base ratios in their total genomic DNA. The DNA methylation levels were approx equal in the three cell lines. Findings obtained with HPLC and those obtained by other techniques are discussed. (16 Refs)

CELL SURFACE PHENOMENA OF TRANSFORMATION

39. PERICELLULAR MATRIX AND CELL SURFACE GLYCOPROTEINS OF VIRUS-TRANSFORMED MOUSE EPITHELIAL CELLS.

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Cancer Res; 42(3):1147-1153 1982

Mouse embryo Mus musculus castaneous epithelial cells, transformed with Moloney murine sarcoma virus (MSV) or with ecotropic murine leukemia virus (MuLV), were analyzed for production of pericellular matrix glycoproteins. The nontransformed, MSV-transformed, and MuLV-transformed cells produced fibronectin, laminin, Type I collagen, and small amounts of Type III collagen when studied by immunofluorescence using specific antibodies. The virus-transformed epithelial cells produced enhanced amounts of fibronectin into their growth media. Nontransformed M musculus castaneous epithelial cells mainly produced Type I collagen, as shown by metabolic labeling and polypeptide analysis. A significant increase in the glycoprotein production was seen by the MuLV-transformed cells, whereas small changes in the collagen production were apparent after MSV transformation. MuLV-transformed cells produced increased amounts of Type I collagen and also some collagenous polypeptides that comigrated with procollagen Type IV chains. The ratio of the procollagen Type I chains deposited in the matrix was altered in transformed cells. Radioactive sur face labeling of the cells revealed changes of the high-mol-wt glycoproteins in both the MSV-and the MuLV-transformed cells. Unlike virus-transformed fibroblastic cells, these transformed epithelial cells deposited and retained connective tissue glycoproteins in their pericellular matrices. The results indicate that viral transformation modulates the pericellular matrix and surface glycoproteins of cultured mouse epithelial cells. The ability of virus-transformed epithelial cells to deposit pericellular matrices is a major difference between them and virus-transformed fibroblastic cells. (Author abstract) (46 Refs)

40. FIBRONECTIN DISTRIBUTION PATTERN AND THE THREE-DIMENSIONAL GROWTH BEHAVIOR OF MAMMALIAN CELLS UNDER ANCHORAGE-INDEPENDENT CONDITIONS.

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Exp Cell Biol; 50(1):2-12 1982

Several types of normal diploid cells, established 'normal' cells, and transformed cells of human and rodent origin have been studied with reference to cell surface fibronectin distribution and their anchorage-independent growth behavior. All cell types that showed intercellular and fibrillar surface fibronectin were anchorage-dependent for growth. Lack of surface fibrillar fibronectin in spontaneously or virus-transformed cells and cells of neoplastic origin was accompanied by anchorage-independent growth potential. The degree of three-dimensional organization of cells under anchorage-independent growth conditions was dependent on the amount of intercellular fibronectin. The significance of these observations to in vivo tumor growth is discussed. (Author abstract) (21 Refs)

41. TRANSFORMATION-DEPENDENT LOSS OF THE HYALURONATE-CONTAINING COATS OF CULTURED CELLS.

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J Cell Physiol; 110(2):123-128 1982

Coats of a variety of cell types, including a rat fibrosarcoma (RFS) cell line which is known to synthesize large amounts of hyaluronate, and two sets of parent and virus-transformed cell lines [Swiss 3T3 vs Simian virus-3T3 cells and baby hamster kidney cells (BHK) vs polyoma-BHK] were studied. Cell coat size was determined by comparing the pattern of settled RBC on control cultures with that of streptomyces hyaluronidase-treated cultures. The cell coat of RFS cells was quite large, as much as 25 um thick in places. The coats of 3T3 and BHK cells were also readily apparent although somewhat smaller than that of RFS cells. In virus-transformed cells, the coats were either greatly reduced or absent. RFS cells had the largest amount of hyaluronate followed in order by the 3T3 and the BHK cells. The two virus-transformed cell lines had much less hyaluronate than their parental counterparts. Differences between the amoun ts of hyaluronate were also reflected in the amounts of hyaluronate secreted into the medium. Cell lines with large coats tended to retain a greater fraction of total hyaluronate at their surfaces. In chemical studies of cells grown in the presence of 3H-glucosamime, the specific activity of the hyaluronate varied considerably from cell line to cell line, with the highest values being obtained from virus-transformed cells. The results indicated that, at least in the case of 3H-glucosamine, incorporation of radioactivity is not a reliable index of the net production of hyaluronate. It was concluded that virus transformation leads to a decrease in the size of the hyaluronate coat of 3T3 and BHK cells. (33 Refs)

42. THE COOPERATIVE ROLE OF THE TRANSFORMATION-SENSITIVE GLYCOPROTEINS, GP140 AND FIBRONECTIN, IN CELL ATTACHMENT AND SPREADING.

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J Biol Chem; 257(6):3249-3257 1982

The detergent-insoluble matrix of cultured human fibroblasts contains cytoskeletal and nuclear components, as well as two major, noncollagenous glycoproteins, fibronectin and GP140. These glycoproteins are stabilized by extensive intermolecular disulfide bonding. GP140 was partially purified, and a higher yield of GP140 could be obtained under reducing conditions by extraction with urea-dithiothreitol followed by molecular sieve chromatography. The purified GP140 contained mannose, galactose, and N-acetylgucosamine residues. Amino acid analysis of GP140 detected periodate-sensitive residues, as well as hydroxylproline. These hydroxylated amino acids are major components of collagens and collagen-like proteins. The GP140 isolated under nonreducing conditions was found to induce stable cell attachment and cell spreading when coated on plastic surfaces. The cell attachment could not be inhibited with affinity purified anti-fibronectin antibodies. However, trypsinization of cells under conditions that removed surface fibronectin reduced the ability of the cells to bind to the GP140-coated surface. Metabolic labeling of cells with radioactive glucosamine during 1-hr cell attachment experiments incorporated label into both fibronectin and GP140, indicating that the cells rapidly glycosylate both fibronectin and GP140 and incorporate them into the stable detergent-insoluble matrix. Long term labeling and chase experiments indicated that fibronectin and GP140 in the matrix are subject to very slow turnover. Neither fibronectin nor GP140 were detectable in the detergent-insoluble matrix of SV40-transformed human fibroblasts by either metabolic or cell surface labeling. These results are consistent with the conclusion that fibronectin and GP140 may function in a cooperative manner in cell adhesion and spreading. (70 Refs)

43. RECEPTOR-ASSOCIATED CHANGES OF THE CATECHOLAMINE-SENSITIVE ADENYLATE CYCLASE IN GLIOMA CELLS DOUBLY TRANSFORMED WITH MOLONEY SARCOMA VIRUS.

Higashida H, Miki N, Tanaka T, Kato K, Nakano T, Nagatsu T, Kano-Tanaka K
Cancer Res. Inst., Kanazawa Univ., Kanazawa 920, Japan
J Cell Physiol; 110(2):107-113 1982

Activity of adenylate cyclase (AC) and the receptor binding assay of 3H-dihydroalprenolol (DHA) for the beta-adrenergic receptor of C6 glioma cells doubly transformed with Moloney sarcoma virus (C6V-1 cells) were carried out as a model system for viral modification of the plasma membrane and compared with those of C6 cells. Intracellular cyclic AMP levels and intracellular phosphodiesterase, mitochondrial monoamine oxidase, and cytosomal enolase activities were measured in both cell lines. C6V-1 cells differed from C6 cells morphologically. C6V-1 cells were composed of large numbers of both round and fusiform cells, whereas C6 cells contained predominantly fusiform cells. C6V-1 cells grew faster than C6 cells with mean doubling times of 17 and 22 hr, respectively. The basal activity of AC was always lower in C6V-1 cells than in C6. Effects of Mg++, prostaglandin E1, isoproterenol, and norepinephrine on AC activity were determined in both cell lines. Fewer DHA binding sites were observed in C6V-1 cells than in C6 cells. Intracellular cyclic AMP content in C6 and C6V-1 cells was 10.1 and 4.4 picomoles/mg protein, respectively. Phosphodiesterase activity in C6 cells was 3x greater than that in C6V-1 cells, with mean activities of 91 and 31 picomoles/mg protein, respectively. Both cell types showed type A mitochondrial monoamine oxidase activity in the range of approx 70-90 picomoles/min/mg protein. Enolase activity was higher in C6V-1 cells than in C6 cells, with specific activities of 1.6 and 2.3 units/mg protein, respectively. (30 Refs)

44. ALPHA2HS GLYCOPROTEIN BINDS TO LYMPHOCYTES TRANSFORMED BY EPSTEIN-BARR VIRUS.

Lewis JG, Crosier PS, Andre CM
Dept. Clinical Biochemistry, Christchurch Clinical Sch. Medicine, Christchurch Hosp., Christchurch, New Zealand
FEBS Lett; 138(1):37-39 1982

Binding of alpha2HS glycoprotein to Epstein-Barr virus (EBV)-transformed peripheral blood lymphocytes was studied by indirect immunofluorescence and by direct counts of cell-bound 125I-alpha2HS glycoprotein. This glycoprotein binds appreciably to EBV-transformed, but not to normal autologous, untransformed, lymphocytes (dissociation constant 5.0 x 10(-7) M, with 0.5 x 10(6) sites/cell). Binding of transformed cells is not blocked by deoxyribonuclease pretreatment, but can be partially blocked by ribonuclease or pronase pretreatment. (11 Refs)

45. LESS MEMBRANE-ASSOCIATED ACTIN IN TRANSFORMED VERSUS NORMAL RAT KIDNEY CELLS.

Rubin RW, Suchard SJ, Ozores JN
Dept. Anatomy, Univ. Miami Sch. Medicine, Miami, FL, 33101
Cell Biol Int Rep; 6(2):177-187 1982

The amount of membrane-associated (MA) actin was compared in normal rat kidney (NRK) cells and their Kirsten viral transformants (442 cells). Entrapment of non-specific proteins and/or chemically induced alterations of plasma membrane incurred during isolation were overcome by employing an isolation procedure which does not require gradient purification, sonication, or the use of chemical membrane stabilizers or detergents. Plasma membranes were isolated by adhering NRK and 442 cells to a poly-L-lysine treated surface, and lysing them with hypotonic buffer. Results showed that MA actin to total MA protein ratio is significantly greater for NRK than for 442 cells. (24 Refs)

46. PHOSPHORYLATION OF VINCULIN BY PP60SRC. WHAT MIGHT IT MEAN?

Hynes R
Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
Cell; 28(3):437-438 1982

Alterations in tyrosine kinase-specific vinculin following infection with Rous sarcoma virus pp60src are described. Vinculin is concentrated at sites of actin-membrane interaction and cell-substratum contact. Pp60src, the transforming protein of Rous sarcoma virus, is concentrated in the same regions. Changes in vinculin, alpha-actinin, and microfilament bundles following transformation are described. (no Refs)

47. CYTOCHEMICAL MARKERS OF BLADDER CARCINOGENESIS.

Wilson PD, Summerhayes IC, Hodges GM, Trejdosiewicz LK, Nathrath WJ
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Histochem J; 13(6):989-1007 1981

Enzyme cytochemical and immunocytochemical techniques were used at the light and electron microscope levels to study the distribution of potential enzyme and antigen markers of chemical transformation in rat and mouse bladders. In in vivo methylnitrosourea-induced rat tumors, alkaline phosphatase (AP) localization was normal on the external surface of the plasma membranes of some cells whereas in others AP was detected only on intracellular membranes. 5'-Nucleotidase (5NU) localization was abnormal in all cells, being seen on endoplasmic reticulum and nuclear membranes only, while in normal bladders only ectoenzyme localization was seen. After tumors were cultured as explants for 15 days, heterogeneity of AP and 5NU localization was seen on the plasma membranes. Enzyme production within some cells was variable while in other cells, only parts of the membrane reacted heavily. A bimodal pattern of AP localization was seen in transformed cell cultures and tumors of mouse bladder derived by in vitro treatment of explants with dimethylbenz(a)anthracene. Cells had either normal ectoenzyme reaction product or abnormal intracellular membrane reaction product. 5NU and adenosine diphosphatase were lost and an Mg.ATPase and a cyclic AMP-independent, calcium-insensitive 'protein phosphatase' were induced in transformed cell cultures. Immunocytochemical study revealed an epithelial antigen in the cytoplasm of both normal and transformed cells which was associated with reticular cytoplasmic ground substance, plasma membrane vesicles and cytoskeletal elements. (29 Refs)

48. EXPRESSION OF HERPES SIMPLEX VIRUS TYPE-COMMON SURFACE ANTIGENS IN CLONAL CELLS OF AN HSV TYPE 2-TRANSFORMED LINE: EFFECT OF ADRIAMYCIN.

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Dept. Periodontology and Endodontology, Sch. Dentistry, Tokushima Univ., Tokushima 770, Japan
Microbiol Immunol; 25(12):1265-1278 1981

The expression of herpes simplex virus (HSV) type-common surface antigen (CSA) was studied in a representative cell clone (155-4-03) of hamster cell line 155-4 transformed by HSV type 2. HSV-CSA was detected by the indirect immunofluorescence test. Expression of HSV-CSA was enhanced by treatment with inhibitors of RNA synthesis (adriamycin [ADM] and daunomycin) but not by inhibitors of DNA synthesis (2-iododeoxyuridine, bleomycin, mitomycin C and cytosine arabinoside), even though all of these agents decreased the number of viable cells in culture to about the same extent. Addition of puromycin or 2-deoxy-D-glucose to ADM markedly suppressed expression of CSA, indicating that both protein synthesis and glycosylation are necessary. ADM enhanced expression of CSA was sensitive to protease inhibitors (antipain and p-nitrophenyl-p'-guanidinobenzoate) and procaine. Procaine affects the organization of the cytoskeletal system (microfilaments and microtubules) in animal cells and also inhibits trypsin. Low concentrations of ADM (0.1 ug/ml) and actinomycin D (0.5 ug/ml) increased CSA expression in an additive manner, while optimal concentrations of each (0.25 and 2.0 ug/ml, respectively) did not. These findings indicate that the two drugs enhance CSA expression in the clone by a common mechanism. (40 Refs)

49. DETECTION OF SIMIAN VIRUS 40 SURFACE-ASSOCIATED LARGE TUMOR ANTIGEN BY ENZYME-CATALYZED RADIOIODINATION.

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Int J Cancer; 29(3):337-344 1982

To facilitate detection of SV40 surface-associated tumor antigen (T-ag), conditions were established to surface label T-ag on intact cells by lactoperoxidase-catalyzed radioiodination (125I/LPO). SDS-PAGE analysis of anti-T immunoprecipitates of SV40-transformed and -infected cells labeled with 125I/LPO revealed the presence of iodinated T-ag. Several types of control experiments were employed to guarantee the surface specificity of the 125I/LPO labeling technique. When SV40-transformed mouse cells were surface labeled with lactoperoxidase and glucose oxidase immobilized on insoluble beads, a preparation less readily internalized than soluble enzymes, T-ag was iodinated. Selective immunoprecipitation of surface antigens demonstrated that lactoperoxidase did not iodinate internally localized T-ag. A reconstruction experiment in which an extract of SV40-infected cells was added to uninfected cells prior to surface labeling suggested that T-ag released from lysed cells did not adhere significantly to monolayer surfaces and become iodinated. Finally, systematic omission of reactants from the iodination reaction revealed that exogenous addition of lactoperoxidase and H2O2 was necessary to generate an iodinated T-ag, indicating that endogenous host cell reactants do not contribute significantly to the iodination of T-ag. 125I-labeled T-ag was detectable on the surface of SV40 tsA-infected cells as the nonpermissive temperature 24 hr postinfection, indicating that the tsA lesion does not prevent the interaction of T-ag with the cell surface. When 125I/LPO-labeled transformed or infected cells were chased for 2.5 hr after labelling, iodinated T-ag was no longer associated with the cell monolayer but was immunoprecipitable from culture supernatants. Cultures from which labeled T-ag had been shed could then be relabeled with 125I/LPO and surface-associated T-ag was again detectable. These data suggest that surface-associated T-ag is continuously shed from the cell surface and is rapidly replaced in the membrane by intracellular T-ag. (Author abstract) (62 Refs)

50. CELL SURFACE MODULATION IN MAMMARY CANCER.

Thompson K
Bruce Lyon Memorial Res. Lab., Children's Hosp. Medical Center, Oakland, CA, 94609
The Handbook of Cancer Immunology: Volume 8- Tumor Antigens: Structure and Function. Waters H, ed. New York, STPM Garland Press, 418 pp., 1981.

Studies of the cell surface modulation which accompanies malignant transformation in mammary cancer are reviewed. Evidence for cell surface antigens (CSAs) of mouse and rat mammary tumors has not shown whether neoplastic transformation is associated with distinct tumor-specific antigens. Virus-induced mouse mammary tumors contain virus-specific antibodies, which are also present in normal mammary cells and nonmammary tissues. In rats with carcinogen-induced mammary tumors, the tumor loses an organ-specific antigen at the time of spontaneous dissemination. The experimental mammary tumors may also show gene derepression, which leads to the expression of abnormal differentiation antigens and/or fetal-type antigens. The tumors can acquire new CSAs not found in the tissue of origin and can acquire or lose CSAs already present in normal cells. Neoplastic transformation is a complex process, especially with regard to the cells which become neoplastic and the influence of host factors (genetic, hormonal, or immunologic). Interaction of these factors determines the malignant state. (283 Refs)

MORPHOLOGICAL AND OTHER BIOLOGICAL ASPECTS OF ONCOGENIC TRANSFORMATION

51. DIFFERENCES IN ANCHORAGE-DEPENDENT GROWTH AND TUMORIGENICITIES BETWEEN TRANSFORMED C3H/10T1/2 CELLS WITH MORPHOLOGIES THAT ARE OR ARE NOT REVERTED TO A NORMAL PHENOTYPE BY ASCORBIC ACID.

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Cancer Res; 42(3):1041-1045 1982

C3H/10T1/2 mouse embryo cells were transformed with 3-methylcholanthrene. Several Type III morphologically transformed cell lines were selected with morphologies that either could or could not be reverted back to normal at passage 1 by daily addition of ascorbic acid (1 or 5 ug/ml). Those transformed cell lines with morphologies that could be caused to revert to normal did not produce colonies in agarose or tumors in nude mice at early passages. Such transformed cell lines at later passages all formed colonies in agarose, but only two of eight lines produced tumors at any passage tested. Subsequently, clones of transformed cells from each cell line have been isolated which are tumorigenic. In contrast, the transformed cell lines which were unresponsive to ascorbic acid at passage 1 were able to form colonies and to produce tumors in early passages. The reversion of the transformed morphology by ascorbic acid is apparently not caused by cytotoxicity since no cell kill was observed following exposure to ascorbate in any newly transformed cell lines at the concentrations used. Thus, the use of ascorbic acid allowed morphologically transformed cell lines to be isolated which appeared to be at different stages in the progression of an initiated cell from a morphologically transformed cell to a highly tumorigenic one. These studies also suggest that low concentrations of ascorbic acid in C3H/10T1/2/CL8 cells can be effective in suppressing oncogenic progression only prior to a stage where an initiated cell achieves the capacity to grow in semisolid medium and to produce tumors in immunosuppressed animals. The importance of these cell lines for elucidating key changes required for the promotion and/or progression of cells to a tumorigenic phenotype is also presented. (Author abstract) (6 Refs)

52. THE RESPONSE OF CHICKEN EMBRYO DERMAL FIBROBLASTS TO CYTOCHALASIN B IS ALTERED BY ROUS SARCOMA VIRUS-INDUCED CELL TRANSFORMATION.

Menko AS, Croop J, Toyama Y, Holtzer H, Boettiger D
Dept. Genetics and Cell Biology, Univ. Minnesota, St. Paul, MN, 55108
Mol Cell Biol; 2(3):320-330 1982

Immunofluorescence and electron microscopy were used to study the effects of cytochalasin B on intermediate filaments and cellular morphology of chick embryo dermal fibroblasts infected with a Rous sarcoma virus mutant (tsLA24A) which is temperature-sensitive for transformation. Effects of c ycloheximide and colcemid on cell morphology at both permissive and nonpermissive temperatures were also studied. Results suggest that intermediate filaments may play a role in cell morphology and that this function is affected by cell transformation. (48 Refs)

53. ALTERATIONS IN MICROFILAMENTOUS AND MICROTUBULAR STRUCTURES ACCOMPANIED BY CELL GROWTH OF SV40-TRANSFORMED CLONAL MACROPHAGES, LINE 28-12 AND ITS SUBLINE.

Katsumoto T
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Cell Struct Funct; 6(4):329-339 1981

Morphological patterns of sets of actively growing and stationary simian virus 40 (SV40)-transformed macrophages of the clonal line 28-12, obtained from SV40-infected cultures of mouse bone marrow cells, were compared with those of the slowly growing subline 28-12(Ara) isolated from cytosine arabinoside-treated cultures. Transmission and scanning electron microscopic observations revealed microfilamentous and microtubular structures in the cells. Bundles of 70 A microfilaments were found in fully-transformed, actively growing 28-12 cells but not in minimally-transformed, stationary 28-12 cells, an observation which inconsistent with other studies. A decrease in microtubules apparently occurs in actively growing cells which have high levels of SV40 T-antigen, although evidence is not unequivocal. Response of the cells to colchicine shows that cytoskeletal structures, including microtubules, are affected by transformation. The 28-12(Ara) cells, which are considered moderately transformed cells, have a significant amount of SV40 T antigen, fewer microtubules than either type of 28-12 cells, lower response to colchicine, and slower growth, but the cells also have a phagocytic capacity. (32 Refs)

54. CONTACT RELATIONSHIPS BETWEEN CHICK EMBRYO CELLS GROWING IN MONOLAYER CULTURE AFTER INFECTION WITH ROUS SARCOMA VIRUS.

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Dept. Zoology, Univ. Coll. London, Gower St., London WC1E 6BT, England
Exp Cell Res; 138(1):147-157 1982

An electron microscopic examination was made of cell contacts and associated microfilament arrays in subconfluent cultures of chick embryo fibroblasts (CEF) and chick embryo retinal pigmented epithelium cells (RPE) transformed by strains of Rous sarcoma virus (RSV) imparting a rounded (Morph r) or fusiform (Morph f) transformed morphology. A few cell substrate contact specializations were found in Morph r-transformed CEF and RPE cells. These resembled cell/substrate plaques of uninfected fibroblasts, but lacked associated microfilament tracts. In contrast Morph f-transformed CEF and RPE resembled untransformed fibroblasts having well developed cell/substrate and cell/cell contact specializations with extensive associated microfilament arrays. Morph r- and Morph f-transformed RPE cells had lost the junctional compl ex typical of untransformed RPE cultures and additionally no melanosomes were found. SEM and TEM demonstrated differences in adhesive properties of CEF and RPE cell surfaces, few virions adhering to the free cell surface of RPE cells but being found in clumps and singly on CEF cells. (Author abstract) (36 Refs)

55. SPECTRUM OF TUMORIGENIC PHENOTYPES AMONG ADENOVIRUS 2-, ADENOVIRUS 12-, AND SIMIAN VIRUS 40-TRANSFORMED SYRIAN HAMSTER CELLS DEFINED BY HOST CELLULAR IMMUNE-TUMOR CELL INTERACTIONS.

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Cancer Res; 42(3):939-944 1982

The tumor-inducing capacities of adenovirus Type 2-, adenovirus Type 12-, and SV40-transformed LSH hamster embryo cells define a spectrum of four distinct tumorigenic phenotypes: Type I, nononcogenic for newborn hamsters but oncogenic for nude mice; Type II, oncogenic for new born hamsters but non-oncogenic in syngeneic adults; Type III, oncogenic for both newborns and syngeneic adults; and Type IV, almost equally oncogenic for syngeneic and allogeneic adult hamsters. Modulation of the cellular immune response of the recipient hamster by immunosuppression or by alloimmunization alters tumor susceptibility, suggesting that dynamic transformed cell-host cellular immune interactions determine the tumorigenic phenotype of a transformed cell line. There is no correlation between the immunogenicities of the transformed cell lines tested and their tumor-inducing capacities. However, a strong correlation exists between the ability of transformed hamster embryo cells expressing Phenotype IV to produce tumors in allogeneic CB hamsters and their resistance to cytolysis in vitro by activated macrophages. These data suggest that, in addition to transformation, DNA viruses may convey specific tumorigenic phenotypes to the cells that they infect by inducing cellular traits that determine the inherent susceptibility or resistance of a cell to host cell-mediated immune destruction. (Author abstract) (29 Refs)

56. IDUR INDUCTION OF A NEW TYPE OF RETROVIRUS-LIKE PARTICLE (EPSILON PARTICLE) IN TRANSFORMED FIBROBLASTIC MOUSE CELLS.

Lasneret J, Canivet M, Bittoun P, Peries J

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Ann Virol; 132(2):151-159 1981

Iododeoxyuridine (IdUr) induced a virus-like structure in fibroblastic BALB/c mouse cells transformed by the Kirsten strain of murine sarcoma virus (Ki-BALB cells). Confluent cultures were treated for 24 hr with 40 ug/ml IdUr and the cells were examined by electron microscopy at 24 and 48 hr post-treatment. No type C virus particles were observed in untreated control cells. IdUr-treated cells showed abundant budding and free C particles and a significant increase in the number of IA particles. A third virus-like particle was observed in treated cells. The structures were spherical with a diameter of 75-85 nanometers and were generally located in the cisternae of rough endoplasmic reticulum. The viral-like particles were observed in groups of 10 or more units and were sometimes intermixed with IA particles. Approx 5% of treated cells contained the particles. The particles were virtually identical to epsilon particles, named for the wheel-like intracisternal structures found in oocytes and early mouse embryos and resembling golden hamster R particles. (17 Refs)

ASSAYS OF ONCOGENIC TRANSFORMATION

57. THE MECHANISM OF ACTION OF CARCINOGENS AND TUMOR PROMOTERS AND THEIR RELEVANCE TO CANCER PREVENTION.

Weinstein IB

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Cancer Research in the People's Republic of China and the United States of America: Epidemiology, Causation and New Approaches to Therapy, Proceedings of a Conference held in New York, 28-29, March, 1980. Marks PA, ed. New York, Grune and Stratton, 273 pp., 1981.

Systems for studying malignant cell transformation in vitro, mimicry of transformation, modulation of differentiation, membrane effects and phospholipid metabolism, membrane receptors for epidermal growth factor and 12-O-tetradecanoyl-phorbol-13-acetate (TPA), synergistic interactions between chemical agents and viruses in cell transformation, molecular mechanism of initiation, and a unified theory of initiation and promotion are discussed. Examples of cell culture systems that can be transformed by chemical carcinogens and by TPA modulation of differentiation are presented. (61 Refs)

58. INDUCTION OF CYTOTOXICITY, MUTATION, CYTOGENETIC CHANGES, AND NEOPLASTIC TRANSFORMATION BY BENZO(A)PYRENE AND DERIVATIVES IN C3H/10T1/2 CLONE 8 MOUSE FIBROBLASTS.

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Cancer Res; 42(5):1866-1875 1982

Benzo(a)pyrene (BaP), a series of its metabolic derivatives, and benzo(e)pyrene, a very weakly carcinogenic isomer, were tested for their biological effects on transformable C3H/10T1/2 cells. These cells were used as targets in a series of assays designed to measure oncogenic transformation, mutation to ouabain resistance, cytotoxicity, and induction of cytogenetic changes, as evidenced by chromosomal aberrations and sister chromatid exchange. Of all the compounds tested, only the parent hydrocarbon, BaP, and (+-)-trans-7,8-dihydroxy-7.8-dihydrobenzo(a)pyrene were found to be significantly active in producing transformation and cytogenetic alterations. BaP, (+-)-trans-7,8-dihydroxy-7.8-dihydrobenzo(a)pyrene, and (+-)-7alpha,8beta-dihydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene however, were all effective inducers of mutation in C3H/10T1/2 cells. (+-)-7alpha,8beta-Dihydroxy-9beta,10beta-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene was the most potent agent in tests for cytotoxicity Benzo(e)pyrene was inactive in all assays examined. Among the compounds tested, there was a correlation between the ability to induce cytogenetic changes and the ability to produce mutation and transformation. These results support the demonstrated role of (+-)-trans-7,8-dihydroxy-7,8-dihydrobenzo(a)pyrene as a proximal carcinogenic form of BaP and illustrate the utility of the C3H/10T1/2 cell system as an important tool for the detection of genotoxic damage by carcinogenic chemicals. (Author abstract) (47 Refs)

59. EXPRESSION OF GENETIC DAMAGE INDUCED BY ALKYLATING AGENTS IN GERM CELLS OF FEMALE MICE.

Becker K, Schoneich J
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Mutat Res; 92(1/2):447-464 1982

The effects of trenimon (TR: 0.25 or 1 mg/kg, ip) and cyclophosphamide (CP: 150 mg/kg, ip) on germ cells were studied in female random-bred NMRI mice (10-13 wk old). Pre-ovulatory treatment with CP or the higher dose of TR caused an increase (significant with TR, slight with CP) in frequency of meiotic non-disjunction in the unfertilized oocytes but did not cause structural aberrations in second-metaphase oocytes. In mice treated with CP or the lower dose of TR before ovulation and mated with random-bred NMRI males up to 0.5 day after treatment, TR showed a strong clastogenic effect on the first-cleavage embryos (first-cleavage metaphase). Numerical and structural chromosome aberrations were observed in 63.39% of the embryos; most of the aberrations were structural aberrations of the chromatid types. The embryonic mortality rate was 55.17%, as measured in the dominant lethal assay. Similar treatment with CP enhanced the occurrence of dominant lethal effects to 58.94%. When the alkylating agents were given at longer times before mating (up to 23.5 days), their clastogenic and mutagenic effects declined with time. The results observed with TR support the conclusion that an intervening round of DNA replication is required for TR-induced DNA damage to be transformed into a structural aberration. (55 Refs)

GENERAL REVIEWS AND OTHER RELATED STUDIES

60. THE NATURE OF CANCER CELLS.

Dulbecco R
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Cancer Research in the People's Republic of China and the United States of America: Epidemiology, Causation and New Approaches to Therapy, Proceedings of a Conference held in New York, 28-29, March, 1980. Marks PA, ed. New York, Grune and Stratton, 273 pp., 1981.

Differences between cancerous and normal cells, ectopic hormones and other proteins, specific cancer changes, cancer markers as replication markers, causes of the majority of irregularities of gene expression in cancer cells, viral carcinogenesis, mechanism of transformation, the transforming gene, genetic events of chemical carcinogenesis, regulation of gene expression in development, initiation, promotion, differentiation, mechanism of the derangement of gene expression in cancer - the role of promotion, other events in progression, a model for carcinogenesis, and consequences of the model are discussed. (43 Refs)

61. REVERSION OF CANCER CELLS.

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Pathol Biol (Paris); 30(3):133-135 1982

Three models of cancer cell reversion are presented, and the following reversion of cells transformed in vitro by oncogenic viruses, collection of normal cells after blockage of differentiation in leukemic cells, and possible differentiation in teratocarcinomas leading to loss of malignancy. In vitro, certain DNA and RNA viruses can transform normal cells into malignant cells with modifications of growth parameters, cellular surface characteristics, cytoskeleton, and nucleotide pool; these virus-transformed cells are capable of tumorigenesis in vivo. Temperature-sensitive mutants of the viral oncogene include normal cells produced from virus-transformed cells. In another model, apparently normal revertant cells may be observed at low frequencies; in vivo, the cells rarely loose their oncogenic potential completely. Dimethylsulfoxide modifies the morphology of Friend's leukemia cells thereby releasing the inhibition that prevents the normal execution of the genetic program; normal differentiation coincides with loss of malignancy. Other leukemia models of reversion are described. Reversion of teratocarcinoma cells is discussed in relation to treatment with retinoids. (no Refs) (In FRE)

62. TUMOR PROMOTION BY REGENERATIVE EPIDERMAL HYPERPLASIA IN MOUSE SKIN.

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J Cutan Pathol; 9(1):1-18 1982

Chemically induced epidermal carcinogenesis is usually divided into two stages: initiation, which involves the conversion of epidermal cells into latent neoplastic cells; and promotion, which allows the expression of this neoplastic change. One of the characteristics of promotion is the transformation of the normal epidermis into a hyperplastic epidermis. One of the unanswered questions about epidermal tumor promotion is whether the epidermal hyperplasia that characterizes promoted skin is simply a regenerative epidermal hyperplasia resulting from damage produced by the promoter. The opinion currently held is that the epidermal hyperplasia produced by tumor promoters is not simply a regenerative epidermal hyperplasia and possesses characteristics which a regenerative hyperplasia does not have, enabling it to evolve into an epidermal neoplasm. The purpose of this review is to present recent evidence which strongly suggests that promoter induced hyperplasia is a regenerative hyperplasia. Two principal lines of evidence are reviewed. Th first demonstrates that an epidermal regenerative hyperplasia repeatedly produced by wounding or abrasion can promote epidermal carcinogenesis in the initiated skin of mice. The second line of evidence demonstrates that the epidermal hyperplasia produced by the application of 12-0-tetradecanoylphorbol-13-acetate (TPA), the most powerful and widely used promoter of skin carcinogenesis, is preceded by damage to the epidermis. This strongly suggests that the epidermal hyperplasia which ensues is a regenerative hyperplasia. The review concludes that during epidermal tumor promotion there is a chronic regenerative epidermal hyperplasia, and that there is no evidence for any other necessary factors during tumor promotion in appropriately initiated mouse skin. (Author abstract) (36 Refs)

63. DNA VIRUSES AND BRAIN TUMOURS.

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Trends Neurosci; 5(1):16-20 1982

Evidence for viral involvement in pathogenesis of some human neurogenic tumors is reviewed. In the case of neurogenic tumor models, direct injection of the virus into the brain eliminates the potential for the host to clear the virus by the immune system. However, certain viruses, such as JCV human papovavirus and adenovirus type 12, can be used to induce intracerebral neoplasms by host infection other than intracerebral injection. Some human viruses (ie human adenovirus type 12 and human papovavirus JCV) are oncogenic both in rodents and in higher primates, however reasons for the differences in oncogenic potential between the various adenovirus serotypes is not known. Locations of the intracellular virus in DNA sequences have not been clearly defined, although some studies indicate that certain viral genes are only found at a limited number of sites; gene cloning techniques should help to evaluate the cellular sites of viral integration and their functions. Other studies suggest that viral genes are essentially fixed in the DNA sequence in virus-induced tumors. However, integrated viral genomes may be lost from transformed cells under certain circumstances. Presence of virus-specific RNA in virus-induced tumor cells is demonstrated by the presence of the so-called tumor(T)-antigen. Etiology of human neurogenic neoplasms is not clear, and proof of a viral etiology of human tumors must largely be circumstantial, yet there are observations that may point to tumor-virus involvement (eg adenovirus) in the pathogenesis of human neurogenic neoplasms. (15 Refs)

64. PROGRESS TOWARDS A UNIFIED THEORY OF THE MECHANISMS OF CARCINOGENESIS, III: CIRCUMVENTION OF PROLIFERATION CONTROLS.

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Med Hypotheses; 8(1):85-93 1982

Examples of mechanisms of carcinogenesis by circumvention of controls over proliferation are presented. RNA tumor viruses produce kinases that are independent of cyclic AMP. These kinases transform most cells by acting on tyrosine residues in several types of proteins. Viral kinases may reduce the efficiency of the sodium pump by modifying a protein component of the pump. The reduction in efficiency may in turn cause the increased glycolysis found in many tumors. Viral kinases may also interfere with actin filaments, affecting contact inhibition of proliferation. Because viral kinases are similar to epidermal growth factor (EGF), they may circumvent EGF requirements for proliferation. Epigenetic modifications of gene expression may be produced by phosphorylation of nonhistone chromosomal proteins. Malignant melanoma cells (MMC) do not produce melanocyte contact inhibitory factor (MCIF), which inhibits growth of tumor cells. MMC produce a similar compound, but do not release this compound. Carcinogenesis may thus result from alteration of the ability of cells to release control factors. Alkylating carcinogens may act by several mechanisms, including interference with methyl transferases, alkylation of DNA, and alkylation of chromosomal proteins. The existence of many possible mechanisms for loss of control of proliferation is indicated, suggesting that no single treatment is possible for all cancers. Understanding the various mechanisms may, however lead to more effective treatments for specific cancers. (26 Refs)

65. A SEARCH FOR SOME COMMON CHARACTERISTICS OF THE EFFECTS OF CHEMICAL MUTAGENS IN DROSOPHILA.

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Mutat Res; 92(1/2):69-87 1982

An analysis of shared general features was used to compare the actions of mutagens in Drosophila. Germ cell metabolism is the most significant factor determining the effects of promutagens in various cell stages. Only autosomal recessive lethal mutations can be used to compare stages sensitivity to a given mutation. Only a few mutagens have been tested in both sexes of Drosophila, including mitomycin C, bleomycin (BLM), and diethylstilbestrol. Females are much more sensitive than males to the mutagenic action of BLM, which causes recessive lethals and X-chromosomal aneuploidy in oocytes. The mutagenicities of some (not all) alkylating agents can be greatly modified by introducing repair-deficient mutants into the test system, but each new strain must be validated before it is tested with a wide variety of mutagens. The molecular mechanisms of the interactions of some methylating and ethylating agents with DNA are related to their genetic effects in germ cells. The relative proportions of chromosome aberrations to mutations and the ability of an agent to induce delayed mutations can be used to provide more information on the basic mechanisms of chemical mutagenesis. For at least some mutagens, a positive correlation has been discovered between the induction of chromosome aberrations in germ cells and the induction of an increased proportion of mosaic twin spots (relative to mosaic single spots) in somatic tissues. (68 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO MAN. SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.
Schmahl D
International Agency for Cancer Research, Lyon, France
IARC Mongr Eval Carcinog Risk Chem Hum 26: 411 pp., 1981.

2. BIOCHEMICAL TOXICOLOGY OF BENZENE.
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Dept. Pharmacology, Thomas Jefferson Univ., Philadelphia, PA, 19107
Rev Biochem Toxicol; 3:123-153 1981

3. A REVIEW OF THE MUTAGENICITY OF CHROMIUM.
Hatherill JR
Toxicology, Sch. Public Health, Univ. Michigan, Ann Arbor, MI, 48109
Drug Chem Toxicol; 4(3):185-195 1981

4. HORMONES AND BREAST CANCER.
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Dept. Family and Preventive Medicine, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Banbury Rep 8: 491 pp., 1981.

5. ORAL CONTRACEPTIVES: VOLUME 5.
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Oral Contraceptives: Volume 5. St. Albans, VT, Eden Medical Research Inc., Annual Research Reviews--Endocrinology, 331 pp., 1981.

6. EPIDEMIOLOGICAL STUDIES OF THE ROLE OF EXOGENOUS ESTROGENS IN THE ETIOLOGY OF BREAST CANCER.
Kelsey JL, Bulbrook RD, Korenman SG, Siiteri PK, Henderson BE
Dept. Epidemiology and Public Health, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Banbury Rep; 8:215-228 1981

7. EFFECTS OF LONG-TERM EXPOSURE TO LOW LEVELS OF OZONE: A REVIEW.
Melton CE
Civil Aeromedical Inst., Federal Aviation Admin., Oklahoma City, OK, 73125
Aviat Space Environ Med; 53(2):105-111 1982

8. METABOLIC INTERACTIONS OF HYDROCARBONS WITH MAMMALIAN LUNG.
Smith BR, Bend JR
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, NIH, Research Triangle Park, NC, 27709
Rev Biochem Toxicol; 3:77-122 1981

9. REVIEW OF EXPERIMENTAL CARCINOGENESIS BY COMPOUNDS RELATED TO VINYL CHLORIDE.
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NCI, Bethesda, MD, 20205
Environ Health Perspect; 41:211-220 1981

10. REVIEWS IN BIOCHEMICAL TOXICOLOGY.
Hodgson E, Bend JR, Philpot RM
North Carolina State Univ., Raleigh, NC
Rev Biochem Toxicol 3: 368 pp., 1981.

DIETARY FACTORS IN CARCINOGENESIS

11. ALCOHOL AND CANCER.
MacSween RN
Univ. Dept. Pathology, Western Infirmary, Glasgow, Scotland
Br Med Bull; 38(1):31-33 1982

12. THE TOXICOLOGY OF COCOA AND METHYLXANTHINES: A REVIEW OF THE LITERATURE.
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Life Sciences, Hershey Foods Corp., Corporate Technical Center, Hershey, PA
CRC Crit Rev Toxicol; 9(4):275-312 1982

13. IMPLICATIONS OF DIETARY FIBER BREAKDOWN IN THE HUMAN COLON.
Cummings JH, Stephen AM, Branch WJ
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Banbury Rep; 7:71-81 1981

14. BILE SALTS AND OTHER CONSTITUENTS OF THE COLON AS TUMOR PROMOTERS.
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Div. Nutrition, American Health Foundation, Naylor Dana Inst. for Disease Prevention, Valhalla, NY, 10595
Banbury Rep; 7:345-363 1981

15. MOLD PRODUCING CARCINOGENIC TOXINS IN FOOD PRODUCTS.
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Internist (Berlin); 23(1):1-9 1982
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Skrabanek P, Walsh A
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23. NONASBESTOS FIBROUS MINERALS.
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Building 512, RMCOEH, Univ. Utah Medical Center, Salt Lake City, UT, 84112
Clin Chest Med; 2(2):203-218 1981

24. REVIEW OF EPIDEMIOLOGIC STUDY RESULTS OF VINYL CHLORIDE-RELATED COMPOUNDS.
Apfeldorf R, Infante PF
Office Carcinogen Identification and Classification, Health Standards, Programs, Occupational Safety and Health Admin. U. S. Dept. Labor, Washington, DC, 20210
Environ Health Perspect; 41:221-226 1981

25. CONCEPTS IN CAUSALITY: CHEMICALLY INDUCED HUMAN URINARY BLADDER CANCER.
Lower GM
Center Human Systems, Inst. Environmental Studies, Univ. Wisconsin, WARF Building, 610 Walnut St., Madison, WI, 53706
Cancer; 49(5):1056-1066 1982

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26. MOLECULAR MECHANISM OF ADAPTATION OF CELLS TO LOW LEVELS OF CARCINOGENIC AGENTS.
Villani G
Laboratoire de Pharmacologie et de Toxicologie Fondamentales, CNRS, 205, route de Narbonne, 31078 Toulouse Cedex, France
Pathol Biol (Paris); 30(2):117-123 1982
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27. MIGHT CANCER BE A FAILED RESPONSE TO RENEGADE MITOCHONDRIA?
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Dept. Anesthesiology, State Univ. New York, Downstate Medical Center, Brooklyn, NY, 11203
J Theor Biol; 94(1):173-178 1982

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Anisimov VN
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29. RELATION OF NEUROLEPTIC DRUGS TO DEVELOPMENT AND GROWTH OF MAMMARY TUMORS.
Meites J, Aylsworth CF
Dept. Physiology, Neuroendocrine Res. Lab., Michigan State Univ., East Lansing, MI, 48824
Banbury Rep; 8:365-376 1981

30. THE ACTIONS OF INSULIN AS A HORMONAL FACTOR IN BREAST CANCER.
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Waterson AP
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33. THE IMMUNOLOGY OF CANCER OF THE HEAD AND NECK WITH PARTICULAR REFERENCE TO ORAL CANCER.
Scully C
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Trosko JE, Chang CC, Warren ST, Liu PK, Wade MH, Tsushimoto G
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Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Scand J Work Environ Health; 7(4):241-251 1981

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Watson DH, Lindsay DG
Food Science Div., Ministry of Agriculture, Fisheries, and Food, Great Westminster House, Horseferry Road, London SW1P 2AE, England
J Sci Food Agric; 33(1):59-67 1982

37. PITUITARY AND STEROID HORMONES IN RADIATION-INDUCED MAMMARY TUMORS.
Shellabarger CJ
Medical Dept., Brookhaven National Lab., Upton, NY, 11973
Banbury Rep; 8:339-351 1981

38. ASPERGILLUS NIDULANS: SYSTEMS AND RESULTS OF TESTS FOR CHEMICAL INDUCTION OF MITOTIC SEGREGATION AND MUTATION. I. DIPLOID AND DUPLICATION ASSAY SYSTEMS. A REPORT OF THE U. S. EPA GENE-TOX PROGRAM.
Kafer E, Scott BR, Dorn GL, Stafford R
Dept. Biology, McGill Univ., 1205 Ave. Docteur Penfield, Montreal H3A 1B1, Canada
Mutat Res; 98(1):1-48 1982

OTHER REVIEWS IN CARCINOGENESIS

39. MATHEMATICAL MODELS OF THE CELL CYCLE WITH A VIEW TO TUMOR STUDIES.
Bertuzzi A, Gandolfi A, Giovenco MA
Centro di Studio dei Sistemi di Controllo e Calcolo Automatici del C.N.R., Via Eudossiana 18, 00184 Rome, Italy
Math Biosci; 53(3/4):159-188 1981

40. NEOPLASMS IN DOMESTIC ANIMALS: A REVIEW OF EXPERIMENTAL AND SPONTANEOUS CARCINOGENESIS.
Madewell BR

Section Clinical Oncology, Dept. Veterinary Surgery, Univ. California, Davis, CA, 95616

Yale J Biol Med; 54(2):111-125 1981

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MECHANISMS OF CARCINOGENESIS

Oncogenic Transformation

SERIES CK14 No. 82/09

SEPTEMBER, 1982

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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TRANSFORMATION GENE STRUCTURE

1. CHANGES IN AMINO-TERMINAL SEQUENCES OF PP60SRC LEAD TO DECREASED MEMBRANE ASSOCIATION AND DECREASED IN VIVO TUMORIGENICITY.

Krueger JG, Garber EA, Goldberg AR, Hanafusa H
Rockefeller Univ., New York, NY, 10021
Cell; 28(4):889-896 1982

We have suggested previously that the amino-terminal 8 kilodaltons of pp60src may serve as a structural hydrophobic domain through which pp60src attaches to plasma membranes. Two isolates of recovered avian sarcoma viruses (rASVs), 1702 and 157, encode pp60src proteins that have alterations in this amino-terminal region. The rASV 1702 src protein (56 kilodaltons) and the 157 src protein (62.5 kilodaltons) show altered membrane association, and fractionate largely as soluble, cytoplasmic proteins in aqueous buffers, in contrast with the membrane association of more than 80% of the src protein of standard avian sarcoma virus under the identical fractionation procedure. Plasma membranes purified from cells transformed by these rASVs contain less than 10% of the amount of pp60src found in membranes purified from cells transformed by Rous sarcoma virus or control rASVs. The altered membrane association of these src proteins had little or no effect on the properties of chick embryo fibroblasts transformed in monolayer culture. In contrast, rASV 1702 showed reduced in vivo tumorigenicity compared with Rous sarcoma virus or with other rASVs that encode membrane-associated src proteins. Rous sarcoma virus-induced tumors are malignant, poorly differentiated sarcomas that are lethal to their hosts. rASV 1702 induces a benign, differentiated sarcoma that regresses and is not lethal to its hosts. These data support the role of amino-terminal sequences in the membrane association of pp60src, and suggest that the amino terminus of pp60src, have a critical role in the promotion of in vivo tumorigenicity. (Author abstract) (14 Refs)

2. GENOME OF RETICULOENDOTHELIOSIS VIRUS: CHARACTERIZATION BY USE OF CLONED PROVIRAL DNA.

Rice NR, Hiebsch RR, Gonda MA, Bose HR, Gilden RV
Biological Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
J Virol; 42(1):237-252 1982

Reticuloendotheliosis virus is an avian Type C retrovirus that is capable of transforming fibroblasts and hematopoietic cells both in vivo and in vitro. Studies have shown that it consists of a replication-competent helper virus (designated REV) that is responsible for transformation. We used restriction endonuclease mapping and heteroduplex analysis to characterize the proviral DNAs of REV-A and REV. Both producer and nonproducer transformed chicken spleen cells were used as sources of REV proviral DNA; this genome was mapped in detail, and fragments of it were cloned in lambdagtWES-lambdaB. The restriction maps and heteroduplexes of the REV and REV-A genomes showed that (i) REV contains a large fraction of the REV-A gag gene; (ii) most or all of REV-A pol is deleted in REV; (iii) REV contains a 1.1 kilobase segment derived from the 3' end of REV-A pol or the 5' end of env or both; (iv) this env region in REV is followed by a 1.9-kilobase segment which is unrelated to REV-A; and (v) the helper-unrelated segment of REV extends essentially all of the way to the beginning of the 3' long terminal repeat. Therefore, REV appears to be an env gene recombinant. We also found that the REV-specific segment is derived from avian DNA, for a cloned Therefore, like the other acute transforming viruses, REV appears to be the product of recombination between a replication-component virus and host DNA. Two other defective genomes in virus-producing chicken cells were also cloned and characterized. One was very similar to REV in its presumptive gag and env segments, but instead of a host-derived insertion it contained additional env sequences. The second was similar to the first in its gag and env regions and appeared to contain an additional 1-kilobase inversion of REV-A sequences. (46 Refs)

3. SUBGENOMIC MRNA IN OK10 DEFECTIVE LEUKEMIA VIRUS-TRANSFORMED CELLS.

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J Virol; 42(1):71-82 1982

OK10, a defective leukemia virus, is produced as a defective particle by so-called nonproducer transformed quail fibroblasts. OK10 defective viral particles contain an 8-kilobases (kb)-long genomic RNA, lack any detectable reverse transcriptase activity, and are not infectious. We studied the genetic content of OK10 RNA extracted from both virions and infected cells. About 77% of the OK10 8.0-kb RNA was related to avian leukosis viruses in the three structural genes gag, pol, and env, as well as in the c region. The remainder of the OK10 genome-encoding capacity was homologous to the MC29-specific transforming sequence myc(m) and has been named myc(o). Heteroduplex molecules formed between the viral OK10 8.0-kb RNA and the 6.8-kb SacI DNA fragment of the Prague A strain of Rous sarcoma virus indicated that the myc(o) sequence formed a continuous RNA stretch of 1.4 to 1.6 kb long between Deltapol and Deltaenv. We also examined the myc(o)-containing mRNA's transcribed in OK10-transformed cells. In OK10-transformed bone marrow cells (OK10 BM), a stable bone marrow-derived cell line producing OK10, the myc(o) sequence was found in four RNA species of 11.0, 8.0, 7.0, and 3.6 kb. Again, the genetic content of these mRNA's indicated that (i) the 3.6-kb species could be spliced out of the 8.0-kb-genome size mRNA and (ii) the 11.0-kb-long mRNA could represent a read-through of the OK10 provirus, the corresponding maturation product being, then, a 7.0-kb mRNA. In conclusion, whereas the myc sequences have been generally thought to be expressed through a gag-onc fusion protein, as for MC29 and CMII viruses, our experiments indicate that they could also be expressed as a non-gag-related product made from a subgenomic mRNA in the OK10 transformed cells. (34 Refs)

4. CELLULAR SEQUENCES RELATED TO THREE NEW ONC GENES OF AVIAN SARCOMA VIRUS (FPS, YES, AND ROS) AND THEIR EXPRESSION IN NORMAL AND TRANSFORMED CELLS.

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Rockefeller Univ., New York, NY, 10021
J Virol; 42(1):143-152 1982

Two onc genes of avian sarcoma viruses unrelated to the src gene have recently been identified: fps of Fujinami sarcoma virus/PRCII/UR1 and yes of Y73/Esh sarcoma virus. In the first part of this study we demonstrated that UR2, the most recently isolated avian sarcoma virus, contains in its genome a unique sequence, ros, nonhomologous to src, fps, and yes sequences or to transforming genes of avian acute leukemia viruses. Using cDNAs specific to the inserts of avian sarcoma virus genomes, we examined the existence and the transcription of cellular nucleotide sequences related to the three new onc genes of avian sarcoma virus (fps, yes and ros) in various cells. The progenitor cellular sequences for these onc genes (c-onc) were present in uninfected chicken DNA in one or few copies per haploid genome. These c-onc sequences were detectable in cellular DNA of a wide variety of vertebrates, and the homology between viral and cellular onc was inversely related to the phylogenetic distance of animal species. The pattern of expression of these c-onc genes in different tissues of chickens was found to be unique to each gene. The expression of c-fps and c-ros genes was generally repressed in many tissues, but c-fps was expressed at higher levels in bone marrow (2.5 copies per cell) and lung (1.1 copies per cell), whereas c-ros was mainly transcribed in kidney (2.5 copies per cell). On the other hand, c-yes transcripts were easily detectable in all tissues analyzed and were found at high levels in kidney (26 copies per cell). These c-onc expressions were unaffected by infection with avian sarcoma viruses that contained other onc genes. In a few cultures of chicken and quail transformed cells derived from tumors induced by chemical carcinogens, we found that the levels of transcription of the four c-onc genes remained unaltered, compared with that in normal tissues. (Author abstract) (60 Refs)

5. TRANSFORMING GENES OF CHICKEN BURSAL LYMPHOMAS.

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J Cell Physiol; Suppl1:209-212 1982

Transforming genes (TG) in chicken bursal lymphomas (BL), isolation of such TG by molecular cloning, and the specificity of TG activated in neoplasms of different types of differentiated cells are discussed. BL are induced in chickens by infection with lymphoid leukosis viruses (LLV). Transfection assays of DNA of LLV-induced BL indicated that these neoplasms contained TG that induced transformation of NIH 3T3 mouse cells with efficiencies of approx 0.1 transformants/ug DNA. No viral sequences were detected in NIH cells transformed by LLV-induced lymphoma DNA using probes either representative of the entire LLV genome or specific for the LLV long terinmal redundancy, which contains the viral transcriptional promoter. TG of BL detected by transfection were linked to viral DNA, indicating that lymphomagenesis by LLV involved indirect activation of cellular TG at some stage of the disease process. DNA of NIH cell transformed by BL cell line RP-9 DNA was subjected to partial digestion with four-base recognition restriction endonuclease Mbo I and cloned in lambda Charon 30 to produce a library of approx 200,000 phage. Restriction fragments of normal chicken DNA were detected in blot hybridization with lambda ChBlym-1 probe indicating that the lambda ChBlym-1 TG is homologous to normal chicken sequences. Analysis of TG of B and T cells neoplasms of mouse and human origin further indicates that specific TG are activated in neoplasms representative of specific stages of lymphocyte differentiation. Results thus indicate that specific TG are activated in neoplasms of particular differentiated cell types and suggests the hypothesis that neoplasia may result from abnormal expression of genes that are normally involved in differentiation-specific growth control. (15 Refs)

6. ENHANCED TRANSFORMATION OF HUMAN FIBROBLASTS BY ORIGIN-DEFECTIVE SIMIAN VIRUS 40.

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Nature; 296(5858):671-672 1982

Wild-type simian virus 40 (SV40) exhibits a low efficiency in transforming semipermissive human fibroblasts (HF). To investigate whether the low efficiency of transformation is related to the ability of SV40 DNA to replicate autonomously in HF, an SV40 mutant defective in the origin of DNA replication (SV ori-) was utilized. A comparison of intact superhelical form I SV40, form I plasmid SV ori+, form I plasmid SV ori-, linear form III plasmid SV ori+, and form III plasmid SV ori- showed that SV ori- DNA was the most efficient in transforming HF as assayed by focus formation in monolayer and colony formation in agarose (anchorage independence). To test the possibility that the enhanced transforming efficiency of SV ori- might be due to the presence of adjoining plasmid sequences and/or modification of DNA through propagation in a bacterial host, the efficiency of transformation by linearized (form III) virion DNA was compared with linear DNAs from SV ori+ and SV ori-, from which plasmid DNA was removed. Again SV ori- was most efficient. However, residual contribution from the bacterial environment (eg methylation) is likely because form III SV ori+ transforms more efficiently than form III SV40. The possibility of secondary infection being responsible for the reduced transforming ability of viral DNA was tested by using DNA from which a late region portion of the genome had been removed, precluding formation of viral particles. In this case, no improvement in transforming ability was observed. These results demonstrate that the efficiency of transformation of semipermissive HF can be enhanced by using a viral DNA defective at the origin of replication. Plasmid SV ori- appears to be a vector of choice for SV40 transformation of human fibroblasts. (22 Refs)

TRANSFORMATION GENE EXPRESSION AND REGULATION

7. STAGE-SPECIFIC TRANSFORMING GENES OF HUMAN AND MOUSE B- AND T-LYMPHOCYTE NEOPLASMS.

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Cell; 28(4):873-880 1982

DNAs of 20 B- and T-lymphocyte neoplasms of human and mouse origin induced transformation of NIH/3T3 cells with high efficiencies, indicating that these neoplasms contained activated transforming genes that were detectable by transfection. Analysis of the susceptibility of the transforming activities of lymphocyte-neoplasm DNAs to digestion with restriction endonucleases indicated that the same or closely related transforming genes were activated in independent neoplasms representative of the same stage of normal cell differentiation. However, different transforming genes were activated in neoplasms representative of different stages of normal B- and T-lymphocyte differentiation. These results indicate that specific transforming genes are activated in neoplasms of discrete stages of differentiation within these cell lineages. (Author abstract) (40 Refs)

8. IDENTIFICATION AND PURIFICATION OF A PROTEIN ENCODED BY THE HUMAN ADENOVIRUS TYPE 2 TRANSFORMING REGION.

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J Virol; 42(1):30-41 1982

The human adenovirus Type 2 (Ad2) transforming genes are located in early regions E1a (map position 1.3 to 4.5) and E1b (map position 4.6 to 11.2). We have identified and purified to near homogeneity a major 20,000-mol-wt (20K) protein and have shown that it is coded by E1b. Using an Ad2-transformed cell antiserum which contained antibody to E1b-coded proteins, we immunoprecipitated 53K and 19K proteins from the nucleoplasm and 53K, 19K, and 20K proteins from the cytoplasmic S-100 fraction of Ad2 productively infected and Ad2-transformed cells. The 19K protein was present in both the nucleoplasm and the cytoplasm, where the 20K protein was found only in the cytoplasm. The 53K and 19K proteins are known Ad2 E1b-coded proteins. The 20K protein was purified to near homogeneity in 20 to 50% yields by sequential DEAE-Sephacel chromatography and reverse-phase high-performance liquid chromatography. Purified 20K protein shares most of its methionine-labeled tryptic peptides with E1b-53K, as shown by reverse-phase high-performance liquid chromatography, and therefore is closely related to the 53K protein. The 19K protein does not appear to share tryptic peptides with either 20K or 53K protein. To provide more direct evidence that 20K protein is virus-coded we translated E1b-specific mRNA in vitro. Both immunoprecipitation analysis and high-performance liquid chromatography purification of the translated product identified a 20K protein that has the same tryptic peptides as the 20K protein isolated from infected and from transformed cells. These findings suggest that the Ad2 20K protein is a primary translation product of an Ad2 E1b mRNA. (Author abstract) (39 Refs)

9. CANDIDATE PRODUCT OF THE FBJ MURINE OSTEOSARCOMA VIRUS ONCOGENE: CHARACTERIZATION OF A 55,000-DALTON PHOSPHOPROTEIN.

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J Virol; 42(1):114-122 1982

Sera from rats bearing tumors induced by inoculation of FBJ murine osteogenic sarcoma virus (FBJ-MSV) nonproducer rat cells precipitate two proteins with mol wt of 55,000 (p55) and 39,000 (p39) from FBJ-MSV-transformed cells. These proteins cannot be precipitated from uninfected cells or cells transformed by other strains of murine sarcoma virus, nor can they be precipitated by sera specific for the viral structural proteins. A methionine tryptic peptide mapping analysis showed that p55 and p39 have little or no homology and that they are not related to the helper virus gag and env gene products. p55 could also be detected among the in vitro translation products of 70S RNA from FBJ murine leukemia virus plus FJB-MSV virions but not among those from FBJ murine leukemia virus alone. This suggests that p55 is encoded by the FBJ-MSV genome, whereas p39, which was not detected among the in vitro translation products, may not be virus encoded. Another difference between p55 and p39 is that p55 is phosphorylated, with most of the phosphate on a serine residue(s), whereas p39 is phosphorylated to a much lesser extent, if at all. No protein kinase activity was associated with p55 and p39 immune complexes under standard conditions. Our data suggest that p55 is a strong candidate for the FBJ-MSV oncogene product. (Author abstract) (32 Refs)

10. DIFFERENTIAL EXPRESSION OF THE AMV GENE IN HUMAN HEMATOPOIETIC CELLS.

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Proc Natl Acad Sci USA; 79(7):2194-2198 1982

Total cellular RNAs from a variety of fresh and culture-derived human hematopoietic neoplastic cell types at various stages of differentiation and human sarcoma, carcinoma, melanoma, and glioblastoma cell lines were enriched for poly(A)-containing sequences, fractionated by gel electrophoresis, and blot hybridized to a cloned DNA probe containing the transforming sequences (v-amv) of avian myeloblastosis virus (AMV), a virus known to cause myeloid leukemias in chickens. Expression of RNA sequences homologous to AMV was detected in all immature myeloid and lymphoid T cells in addition to single erythroid cell line examined, but not in mature T cells or in B cells, including lymphoblast cell lines derived from patients with Burkitt lymphoma. In addition, induction of the cell line HL60, a promyelocytic leukemia line, to differentiate with dimethyl sulfoxide or retinoic acid resulted in a reduction of the level of expression of the human cellular gene c-amv homologous to v-amv. There was no detectable c-amv mRNA in any of the solid tumor cell lines examined. Thus, expression of the human c-amv gene could be correlated with the stage of differentiation of different hematopoietic cell types determines by morphologic and marker studies. Expression of c-amv could not be correlated with the extent of methylation in HL60 and in HL60 induced to differentiate with dimethyl sulfoxide. (Author abstract) (48 Refs)

11. ACTIVATION OF AN ENDOGENOUS MOUSE TYPE C VIRUS BY UV-IRRADIATED MURINE CYTOMEGALOVIRUS.

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Int J Cancer; 29(4):459-464 1982

Infection of Kirsten sarcoma virus-transformed non-producer BALB-3T3 mouse cells with UV-irradiated mouse cytomegalovirus (MCMV) resulted in activation of a xenotropic Type C virus detected by infectious center formation in permissive rat or mink cells. The levels of Type C virus activated by MCMV were related to the UV dose applied. Under optimal conditions the frequencies of activation varied from 3.0 to 8.0 x 10(-4). The capacity of MCMV to activate Type C virus was abolished by heat inactivation and by neutralization with specific antiserum against MCMV. Virus induction decreased under conditions of cell exposure to hydroxyurea or actinomycin D, inhibitors of DNA and RNA synthesis, respectively, with actinomycin D having a greater inhibitory effect. This suggests that both DNA and RNA synthesis are required for UV-MCMV induction of murine xenotropic virus. (Author abstract) (33 Refs)

12. TRANSFORMATION-DEFICIENT ADENOVIRUS MUTANT DEFECTIVE IN EXPRESSION OF REGION 1A BUT NOT REGION 1B.

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J Virol; 42(1):106-113 1982

An adenovirus Type 5 host range mutant (hr440) has been isolated which is defective in a splicing event required to generate the middle-sized mRNA from early region 1A. This defect has been ascribed to two adjacent nucleotide changes which lie five and six nucleotides from the 5' splice site for this mRNA. One of these changes introduces an amber codon into the reading frame of the largest region 1A mRNA, resulting in the production of a truncated polypeptide. Like other region 1A mutants, hr440 is defective in the production of mRNA from early regions 2 and 3, but hr440 is unusual in that transcription from regions 1B and 4 is normal. Furthermore, although region 1B expression is unaffected, hr440 does not transform baby rat kidney cells. Therefore, expression of early region 1B is insufficient for transformation, eliminating the possibility that region 1A is required only to induce such expression. (Author abstract) (41 Refs)

13. POLYPEPTIDES ENCODED BY TRANSFORMING REGION E1B OF HUMAN ADENOVIRUS 2: IMMUNOPRECIPITATION FROM TRANSFORMED AND INFECTED CELLS AND CELL-FREE TRANSLATION OF E1B-SPECIFIC MRNA.

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Virology; 118(2):456-465 1982

We have identified polypeptides specific to region E1b (map position [mp] 4.6-11.2) of adenovirus 2 (Ad2) that are synthesized in six lines of Ad-transformed rat or human cells (F17, F4, T2C4, 8617, 5RK clone I, 293), and in Ad2 early infected KB cells. [35S]Methionine-labeled polypeptides were immunoprecipitated using antisera against F17 cells, an Ad2-transformed rat cell line that retains only E1. To determine whether they are viral coded, these polypeptides were compared by tryptic peptide mapping with polypeptides translated in vitro from Ela-specific mRNA (mp 1.3-4.5) and Elb-specific mRNA. Polypeptides of 19,000 daltons (19K), 20K, and 53K were immunoprecipitated from Ad2 early infected KB cells. The 19K, 20K, and 53K could be translated from Elb-specific mRNA and thus are coded by Elb. The 19K was precipitated from all transformed cell lines, the 20K was immunoprecipitated from F4, 8617, and T2C4 cells, and the 53K was immunoprecipitated from F4, 8617, T2C4, and 293 cells. These results suggest that the 19K, and perhaps the 20K and 53K, may be important in adenovirus-induced cell transformation. The 20K and 53K share methionine-containing tryptic peptides with each other, but not with the 19K. These results, together with the Ad2 Elb DNA sequence suggest that 19K is translated in a different reading frame from 53K and 20K. (Author abstract) (39 Refs)

14. IDENTIFICATION OF A FISH PROTEIN ASSOCIATED WITH A KINASE ACTIVITY AND RELATED TO THE ROUS SARCOMA VIRUS TRANSFORMING PROTEIN.

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Cancer Res; 42(6):2429-2433 1982

Cells of all vertebrates thus far investigated contain a cellular src gene, which appears to be a highly conserved homolog of the Rous sarcoma virus oncogene src. Similar to the Rous sarcoma virus oncogene src, this endogenous cellular src gene codes for a Mr 60,000 phosphoprotein (pp60c-src) which is associated with a kinase activity. This kinase specifically phosphorylates tyrosine residues of proteins. We have systematically looked for pp60c-src in specific strains of certain teleostean fish, including the genera Xiphophorus and Girardinus. These strains are known to contain chromosomal oncogenes causing neoplastic transformation in certain mutants and hybrids. Since the pp60c-src found in other species has been shown to be antigenically related to the viral src gene product, a phosphoprotein with a molecular weight of 60,000 (pp60r-src), we have used tumor-bearing rabbit serum which recognizes Rous sarcoma virus pp60src to detect such a related protein in fish. Tumor-bearing rabbit serum precipitated two proteins with molecular weights of 60,000 and 52,000. The Mr 60,000 phosphoprotein was associated with a protein kinase activity that phosphorylates tyrosine residues of the immunoprecipitating immunoglobulin G heavy chain (Mr 53,000). The antigenic relationship of this fish protein to viral pp60src was further documented by an immune competition assay. We conclude, therefore, that the fish Mr 60,000 phosphoprotein is a pp60c-src encoded for by a fish cellular src gene that corresponds to the viral src oncogene. The Mr 52,000 phosphoprotein is probably a proteolytic degradation product of pp60c-src. All animals of the various strains of the fish investigated in this study showed kinase activity that was reactive upon immunoprecipitation with tumor-bearing rabbit serum, indicating that the pp60c-src protein is a normal constituent of the fish. Measurable quantitative differences were revealed between the various strains as well as in different tissues. Whereas brain and melanoma tissue showed a high kinase activity when compared to skin, liver, spleen, and testes, muscle tissue displayed no significant activity. (Author abstract) (27 Refs)

15. IDENTIFICATION OF A PHOSPHOPROTEIN SPECIFICALLY INDUCED BY THE TRANSFORMING DNA OF RAT NEUROBLASTOMAS.

Padhy LC, Shih C, Cowing D, Finkelstein R, Weinberg RA
Center Cancer Res., Cambridge, MA, 02139
Cell; 28(4):865-871 1982

DNAs from nitrosoethylurea-induced rat neuroblastomas transform NIH/3T3 mouse fibroblasts in a transfection assay. DNAs of such transformed cells can be used in a subsequent cycle of transfection to generate secondary foci that contain virtually no foreign genetic material besides the sequences carrying the rat neuroblastoma transforming function. These secondary neuroblastoma transfectants were injected into young mice and grew out into fibrosarcomas. Sera from these mice were examined for reactivity with any proteins which were induced specifically by the neuroblastoma transforming sequence. These sera precipitate a polypeptide of about 185,000 daltons from 35S-methionine-labeled cell lysates of the rat neuroblastoma cells that served as DNA donors and in all transfection-drived primary and secondary foci. This protein is present in high levels in all neuroblastoma transfectant clones, but was not detectable in a variety of other transformed cells. Antisera were prepared from mice bearing tumors induced by transformed cells derived by transfection of DNAs from various tumor cell types unrelated to rat neuroblastoma. These antisera failed to immunoprecipitate the 185,000 dalton protein. These data indicate that the synthesis of the 185,000 dalton protein is specifically induced by the neuroblastoma transforming sequence. The protein may be encoded by the transforming sequence and may mediate transformation in this chemically induced tumor. (Author abstract) (9 Refs)

16. A CELLULAR PROTEIN IS IMMUNOLOGICALLY CROSSREACTIVE WITH AND FUNCTIONALLY HOMOLOGOUS TO THE FUJINAMI SARCOMA VIRUS TRANSFORMING PROTEIN.

Mathey-Prevot B, Hanafusa H, Kawai S

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Cell; 28(4):897-906 1982

We obtained a regressing-tumor antiserum specific for the unique sequence of the transforming protein P140 of Fujinami sarcoma virus by injecting Fischer rats with syngeneic embryo cells transformed with Fujinami sarcoma virus. This serum is capable of immunoprecipitating a protein of 98,000 daltons from cell extracts of normal, uninfected chicken bone marrow cells. This normal cellular protein (NCP98) was shown to be structurally related to P140, sharing the majority of 35S-methionine-labeled tryptic peptides with the viral gene product P140. NCP98 is a phosphoprotein in vivo, with an association in vitro protein kinase activity, capable of phosphorylating specifically at tyrosine residues of NCP98 itself and alpha-casein, an externally added substrate. This kinase activity is biochemically indistinguishable from the kinase activity is biochemically indistinguishable from the kinase activity associated with P140 by all criteria tested. Moreover, in vitro-phosphorylated NCP98 and P140 shared the same phosphopeptides. The expression of NCP98 is tissue-specific. It is readily detectable in bone marrow cells and detectable to a lesser extent in liver and lung cells from 6-18 day old chickens. (Author abstract) (44 Refs)

17. MOLECULAR BIOLOGY CRITERIA FOR THE FUNCTION OF ROUS SARCOMA VIRUS GENE IN TRANSFORMED KHS RAT CELLS.

Kiselev FL, Galetskii SA, Mazurenko NN, Asanova AA, Zborovskaia IB, Topol' LZ

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Mol Biol (Mosk); 16(1):66-76 1982

Integration, transcription and translation of Rous sarcoma virus (RSV) genome was studied in (non-virus-producing) transformed rat fibrosarcoma XC cells. About 10 copies of RSV genome were integrated into the host cell genome. Different types of viral RNAs, identified in the cytoplasmic fraction, had sedimentation values similar to those for RSV-specific RNAs in virus-producing chicken cells. These RNAs were translated in polysomes and directed the synthesis of gag, env and src proteins. Compared with chicken cells, the cleavage of gag precursor Pr 76gag was not observed in transformed XC cells. (30 Refs) (In RUS)

18. HALF-LIFE OF THE ROUS SARCOMA VIRUS TRANSFORMING PROTEIN PP66SRC AND ITS ASSOCIATED KINASE ACTIVITY.

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Mol Cell Biol; 2(4):355-360 1982

Chick embryo cells infected with the Prague A strain of Rous sarcoma virus and several transformation-defective, temperature-sensitive mutants were pulse-labeled with [35S]methionine; the half-lives of metabolically labeled pp60src and the associated protein kinase activity were determined. Irrespective of the temperature at which the cells were grown, pp60src had a half-life of approx 60 min in Wild-type and mutant-infected cells. Treatment with cycloheximide, emetine, cordycepin, or puromycin significantly prolonged the half-life of the pp60src-associated protein kinase activity and the half-life of metabolically labeled pp60src. The apparent contradiction between the half-lives of the kinase activity and the labeled pp60src protein was resolved by the observation that treatment of cells with inhibitors of protein synthesis stabilized pp60src, resulting in a greatly extended half-life. Since protein synthesis inhibitors also extended the half-life of the gag precursor polypeptide, Pr76, a host factor(s) may be necessary for efficient intracellular processing of the polypeptide to the gag proteins. (30 Refs)

19. AVIAN SARCOMA VIRUS UR2 ENCODES A TRANSFORMING PROTEIN WHICH IS ASSOCIATED WITH A UNIQUE PROTEIN KINASE ACTIVITY.

Feldman RA, Wang LH, Hanafusa H, Balduzzi PC

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J Virol; 42(1):228-236 1982

UR2 is a newly characterized avian sarcoma virus whose genome contains a unique sequence that is not related to the sequences of other avian sarcoma virus transforming genes thus far identified. This unique sequence, termed ros, is fused to part of the viral gag gene. The product of the fused gag-ros gene of UR2 is a protein of 68,000 daltons (P68) immunoprecipitable by antiserum against viral gag proteins. In vitro translation of viral RNA and in vivo pulse-chase experiments showed that P68 is not synthesized as a larger precursor and that it is the only protein product encoded in the UR2 genome, suggesting that it is involved in cell transformation by UR2. In vivo, P68 was phosphorylated at both serine and tyrosine residues. Immunoprecipitates of P68 with anti-gag antisera had a cyclic nucleotide-independent protein kinase activity that phosphorylated P68, rabbit immunoglobulin G in the immune complex, and alpha-casein. The phosphorylation by P68 was specific to tyrosine of the substrate proteins. P68 was phosphorylated in vitro at only one tyrosine site, and the tryptic phosphopeptide of in vitro-labeled P68 was different from those of Fujinami sarcoma virus P140 and avian sarcoma virus Y73-P90. A comparison of the protein kinases encoded by UR2, Rous sarcoma virus Fujinami sarcoma virus, and avian sarcoma virus Y73 revealed that UR2-P68 protein kinase is distinct from the protein kinases encoded by those viruses by several criteria. Our results suggest that several different protein kinases encoded by viral transforming genes have the same functional specificity and cause essentially the same cellular alterations. (Author abstract) (32 Refs)

20. IDENTIFICATION OF A PRECURSOR IN THE BIOSYNTHESIS OF THE P21 TRANSFORMING PROTEIN OF HARVEY MURINE SARCOMA VIRUS.

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J Virol; 42(1):253-261 1982

The p21 transforming protein coded for by the v-ras gene of Harvey murine sarcoma virus (Ha-MuSV) migrates as a doublet band between 21,000 and 23,000 daltons during sodium dodecyl sulfate-polyacrylamide gel electrophoresis. The lower band of the doublet is designated p21, and the upper band is designated pp21 since it comigrates with the phosphorylated form of p21. By pulse-labeling with [35S]methionine, we detected a p21 precursor, pro-p21, which migrated as if it was approx 1,000 daltons larger than p21. The precursor-product relationship was established by pulse-chase experiments with [35S]methionine in the presence of 100 ug of cycloheximide per ml, which inhibited all de novo protein biosynthesis. Within 4 h, pro-p21 was completely chased into p21, and during the next 24 h pp21 accumulated. Thus, formation of pp21 from p21 did not require de novo protein synthesis. By subcellular fractionation into cytosol and membrane fractions, we found that pro-p21 was synthesized in a non-membrane-bound state and that shortly after its complete synthesis, the p21 product was associated with the membrane fraction. By selective cleavage of p21 at a unique aspartic acid-proline residue with 70% formic acid or with Staphylococcus aureus V8 protease, we found that the intramolecular site of pro-p21 processing was located in the C-terminal portion of the pro-p21 molecule. The possibilities that the precursor was involved in the assembly of p21 into the plasma membrane and, alternatively, that the processing was a step in the activation of p21 biochemical activities are discussed. (Author abstract) (18 Refs)

21. CONSTRUCTION OF PLASMIDS FOR EXPRESSION OF ROUS SARCOMA VIRUS TRANSFORMING PROTEIN, P60SRC, IN ESCHERICHIA COLI.

Gilmer TM, Parsons JT, Erikson RL
Dept. Pathology, Univ. Colorado Sch. Medicine, Denver, CO, 80262
Proc Natl Acad Sci USA; 79(7):2152-2156 1982

We have constructed plasmids that direct the synthesis of the Rous sarcoma virus transforming gene (src) product (p60src) in Escherichia coli. A 203-base-pair lac promoter-operator DNA encoding the first eight amino acids or beta-galactosidase was ligated to the 5' end of the src gene from the Prague A strain of Rous sarcoma virus (PrA-RSV) which had been cloned in pBR325. Antiserum, from a tumor-bearing rabbit, directed against pp60src was used to screen bacteria containing the recombinant plasmid for a protein of approx 60,000 daltons, and several colonies producing a protein immunologically related to pp60src were detected. Partial proteolytic cleavage analysis revealed that the src-related protein produced in bacteria is structurally similar to pp60src immunoprecipitated from PrA-RSV-infected chicken cells. Partially purified src protein from E coli can be phosphorylated in vitro by the catalytic subunit of cAMP-dependent protein kinase. Tryptic phosphopeptide analysis demonstrated that the catalytic subunit phosphorylated a serine-containing tryptic peptide in the bacterial src protein that comigrated with the phosphoserine-containing tryptic peptide of pp60src immunoprecipitated from 32P-labeled PrA-RSV-infected chicken cells. (Author abstract) (31 Refs)

GENETIC AND OTHER HOST FACTORS WHICH MODULATE ONCOGENIC TRANSFORMATION

22. INTEGRATED ADENOVIRUS TYPE 12 DNA IN THE TRANSFORMED HAMSTER CELL LINE T637: SEQUENCE ARRANGEMENTS AT THE TERMINI OF VIRAL DNA AND MODE OF AMPLIFICATION.

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(c/o Doerfler) Inst. Genetics, Univ. Cologne, Cologne, W. Germany
J Virol; 42(1):317-321 1982

Approx 20 to 22 copies of adenovirus Type 12 (Ad12) DNA per cell were integrated into the genome of the cell line T637. Only a few of these copies seemed to remain intact and colinear with virion DNA. All other persisting viral genomes exhibited deletions or inversions or both in the right-hand part of Ad17 DNA. Spontaneously arising morphological revertants of T637 cells had lost viral DNA. In most of the revertant cell lines only the intact or a part of the intact viral genome was preserved; other revertant cell lines had lost all viral DNA. In three other Ad12-transformed hamster cell lines, HA12/7, A2497-3, and CLAC3, major rearrangements at the right end of the integrated Ad12 DNA were not found. These studies were performed to investigate the phenomena of amplification, rearrangements, and deletions of Ad12 DNA in hamster cells. (Author abstract) (16 Refs)

23. DIFFERENTIATION AND VIRUS EXPRESSION IN BALB/MO MICE: ENDOGENOUS MOLONEY LEUKEMIA VIRUS IS NOT ACTIVATED IN HÉMATOPOIETIC CELLS.

Fiedler W, Nobis P, Jahner D, Jaenisch R
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Proc Natl Acad Sci USA; 79(6,part1):1874-1878 1982

The endogenous Moloney leukemia virus (M-MuLV) in the BALB/Mo substrain of mice is activated during the 1st wk after birth. Virus replication occurs in cells of the lymphatic system. Lymphoid cells therefore represent the target cells for virus replication and leukemic transformation. To investigate whether virus activation occurs during lymphoid cell differentiation, hematopoietic stem cells carrying the endogenous Mov-1 genome were transplanted to sublethally irradiated BALB/c mice. Effective colonization of the recipients was demonstrated by Southern DNA hybridization. No activation of the endogenous Mov-1 genome occurred during a 4-mo observation period after the transplantation. Thus, the first step in development of disease in BALB/Mo mice involves activation of the Mov-1 locus in a nonhematopoietic cell followed by superinfection of lymphatic cells and subsequent virus replication and virus spread. (Author abstract) (20 Refs)

24. FREQUENCY OF UV-INDUCED NEOPLASTIC TRANSFORMATION OF DIPLOID HUMAN FIBROBLASTS IS HIGHER IN XERODERMA PIGMENTOSUM CELLS THAN IN NORMAL CELLS.

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Proc Natl Acad Sci USA; 79(8,part1):2613-2617 1982

If neoplastic transformation of diploid human cells results from carcinogen-induced mutations, cells deficient in excision repair of UV-induced DNA damage should be significantly more sensitive to transformation by UV light than normal cells. We tested this hypothesis by irradiating fibroblasts from a xeroderma pigmentosum patient (XP7BE, complementation group D) with low doses of UV light (254 nm) and cells from a normal person with much higher doses and comparing the frequency of transformation to anchorage independence. Both sets of cells exhibited a dose-dependent increase in transformation which corresponded to a dose-dependent decrease in survival. At doses that caused equal cell killing, the frequency of anchorage-independent cells was approximately equal. Colonies of XP7BE and normal cells isolated from agar, propagated, and injected into x-irradiated athymic mice produced fibrosarcomas in 100% of the animals. Normal cells irradiated shortly before the onset of DNA synthesis exhibited a high frequency of anchorage-independent cells; cells irradiated in early G1 showed no increase over background. These results agree with those we observed for UV induction of 6-thio-guanine-resistant mutants in these cells and support the hypothesis that anchorage independence results from mutations induced by DNA replication on a damaged template. (Author abstract) (21 Refs)

25. VARIATIONS AMONG SPECIES AND CELL TYPES IN THE EFFECTS OF CAFFEINE ON MUTAGEN-INDUCED CYTOTOXICITY AND POSTREPLICATION REPAIR OF DNA.

Sivak A, Rudenko L, Teague LG

Arthur D. Little, Inc., Cambridge, MA, 02140

Environ Mutagen; 4(2):143-162 1982

Caffeine effects in culture of rodent and human cells are reviewed, and the effects of caffeine on postreplication repair induced by chemical mutagens in normal human fibroblasts (HS-WP), human xeroderma pigmentosum fibroblasts (SGL), mouse BALB/c-3T3 fibroblasts, Syrian hamster embryo cells (SHE), and Chinese hamster V79 cells are reported. Cells were exposed to UV light (100 ergs/square mm), nitroquinoline-N-oxide (NQO: 2.5 uM), N-acetoxy-N-2-fluorenylacetamide (AFFA: 2.0 uM), and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG: 50.0 uM) and then to caffeine (0.05-1.0 milliM). Cytotoxicity was enhanced by addition of caffeine to V79 cells and BALB/c-3T3 cells after exposure to either UV light or AFAA. Postreplication repair of V79 cells was inhibited in cells exposed to UV and AFFA. Postreplication repair was not affected by caffeine at concentrations up to 1.0 milliM in HS-WP, SGL, SHE and mouse BALB/c-3T3 cells after exposure to UV, AFAA, NQO, or MNNG. Repair in BALB/c-3T3 cells exposed to UV or AFAA was also unaffected. The failure of cytoxicity results to agree with repair results for most of these cells indicates that it is incorrect to use cytotoxicity evidence for caffeine to imply that genetic damage has occurred. (49 Refs)

26. IN VIVO HORIZONTAL ONCOGENESIS BY A HUMAN TUMOR IN NUDE MICE.

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Div. Experimental Pathology, Dept. Pathology, Univ. Kentucky Medical Center, Lexington, KY, 40536

Proc Natl Acad Sci USA; 79(7):2389-2392 1982

A human mucinous cystadenocarcinoma of the ovary was propagated in nude mice. After cryopreservation of the third-passage xenograft for 4 yr, subsequent in vivo transplants showed the emergence of two distinct populations, one resembling the original human adenocarcinoma and the other resembling a spindle-cell sarcoma. These two tumor cell populations were confirmed to be human and murine, respectively, by cytogenetic study, and the epithelial tumor cells were further shown to be of human origin by immunoperoxidase staining of blood group A antigen. Separation of the two tumor cell populations in vitro permitted the independent propagation of the human and murine tumor cells in vitro and in vivo. The murine sarcoma was also capable of growth in ordinary BALB/c mice. These results indicate that human cancer cells can induce malignancy in adjacent, putatively normal, cells of nude mice in vivo. (Author abstract) (18 Refs)

27. PARENTAL EXPOSURE TO X RAYS AND CHEMICALS INDUCES HERITABLE TUMOURS AND ANOMALIES IN MICE.

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Inst. for Cancer Res., First Dept. Surgery, Osaka Univ. Medical Sch., Fukushima-ku, Osaka 553, Japan

Nature; 296(5857):575-577 1982

A summary is presented of the effects of radiation (RT) with x-rays and various chemicals in mice studied in multiple generations over a 13-yr period and involving 12,905 live-born mice and 9,645 fetuses from 2,904 parents. There was almost a linear increase in dominant lethals following radiation (RT) of spermatids, spermatozoa, and oocytes. There was no significant increase after treatment of spermatogonia. No increase in dominant lethals was produced by treatment with urethan (U). There was a large and significant increase in anomalies in progeny of parents treated with RT or U; only open eyelid, the predominant non-lethal anomaly, was shown to be transmissible. Both RT and U significantly increased the number of tumors in progeny regardless of which sex was treated. The dose-response data for RT showed a clear increase with dose for treatment of post-meiotic stages in males and less clear results for treatment of spermatogonia. Oocytes at late follicular stages were resistant to 36-108 rad of x-rays but were very sensitive to higher doses. As to site, 87% of induced tumors were in the lung with the remainder in many other sites. To confirm that the induced tumors were heritable, after initial treatment of only the male parent, the F1 progeny of treated parents were mated and their progeny examined. Besides treatment with RT and U, some mice were treated with 4-nitroquinoline 1-oxide. The induced tumors were inherited as if they were dominant mutations with about 40% penetrance. (12 Refs)

28. MECHANISM FOR THE LOSS OF PREFERENTIAL BENZO[A]PYRENE BINDING TO THE LINKER DNA OF CHROMATIN.

Jack PL, Brookes P
Chemical Carcinogenesis Div., Inst. Cancer Res., Pollards Wood Res. Station, Nightingales Lane, Chalfont St. Giles, Bucks HP8 4SP, England
Carcinogenesis; 3(3):341-344 1982

We have examined the fate of the asymmetric chromosomal distribution of DNA adducts generated by the chemical carcinogen r-7,t-8-dihydroxy-t-9,10-oxy-7,8,9,10 tetrahydrobenzo[a]pyrene (BPDE). Treatment of mouse embryo cells with BPDE results in 3.5x more binding to the linker DNA regions between nucleosome cores than to the nucleosome core DNA itself, but 24 hr post-treatment incubation of these cells leads to a loss of this non-random binding. A similar result was obtained when post-treatment incubation was carried out in the presence of hydroxyurea indicating that factors other than DNA replication are responsible for this change in adduct distribution. However in the case of excision repair deficient xeroderma pigmentosum (XP12/BE) cells the non-random adduct distribution was stable over a period of 48 hr, whereas with excision repair proficient XP variant (XP4/BE) cells, loss of preferential binding did occur. These results indicate that the loss of non-random nucleosomal DNA modification with time can be accounted for by the preferential removal of adducts from micrococcal nuclease sensitive linker DNA and further, demonstrates that in certain cells at least, the relative position of nucleosome core structures on DNA remains unchanged over a period of at least 48 hr. (Author abstract) (18 Refs)

29. RESIDENT ENHANCED REPAIR: NOVEL REPAIR PROCESS ACTION ON PLASMID DNA TRANSFORMED INTO ESCHERICHIA COLI K-12.

Strike P, Roberts J
Dept. Genetics, Univ. Liverpool, Liverpool L69 3BX, England
J Bacteriol; 150(1):385-388 1982

The survival of UV-irradiated DNA of plasmid NTP16 was monitored after its transformation into recipient cells containing an essentially homologous undamaged plasmid, pLV9. The presence of pLV9 resulted in a substantial increase in the fraction of damaged NTP16 molecules which survived in the recipient cells. This enhanced survival requires the host uvrA+ and uvrB+ gene products, but not the host recA+ gene product. The requirement for both homologous DNA and the uvrA+ and uvrB+ gene products suggests that a novel repair process may act on plasmid DNA. Possible mechanisms for this process are considered. (Author abstract) (14 Refs)

EXPERIMENTAL MODULATION OF ONCOGENIC TRANSFORMATION

30. REGULATION OF THE CELLULAR P53 TUMOR ANTIGEN IN TERATOCARCINOMA CELLS AND THEIR DIFFERENTIATED PROGENY.

Oren M, Reich NC, Levine AJ
Dept. Microbiology, Sch. Medicine, State Univ. New York at Stony Brook, Stony Brook, NY, 11794
Mol Cell Biol; 2(4):443-449 1982

The regulation of a 53,000-mol wt cellular tumor antigen, p53, in F9 embryonal carcinoma cells was investigated. Treatment of F9 cells with retinoic acid and dibutyryl ADP causes the cells to differentiate, predominantly into endoderm-like cells, and results in a marked decrease in the levels of p53. The mechanism(s) responsible for the decline in p53 in differentiated cells involves a marked decrease in the amount of in vitro translatable p53 messenger RNA. This mechanism is discussed with respect to that operating in simian virus 40 infection or transformation and which involves increased stability of the p53 protein. (22 Refs)

31. ISOLATION OF METHYLCHOLANTHRENE-'INITIATED' C3H/10T1/2 CELLS BY INHIBITING NEOPLASTIC PROGRESSION WITH RETINYL ACETATE.

Mordan LJ, Bergin LM, Budnick JE, Meegan RR, Bertram JS
Dept. Experimental Therapeutics, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Carcinogenesis; 3(3):279-285 1982

A clone of 3-methylcholanthrene-treated 10T1/2 cells has been isolated which possess basic characteristics expected of 'initiated' cells. In the presence of retinyl acetate, this clone exhibits contact inhibited growth control and is morphologically indistinguishable from the parental 10T1/2 cell line. Removal of retinyl acetate in vitro results in neoplastic transformation after a latent period of 3 wk. The classical 10T1/2 transformation system was reconstructed by coculturing normal and 'initiated' 10T1/2 cells. In these cultures 62% of the clonogenic 'initiated' 10T1/2 cells formed either Type III foci after a latent period of 3-4 wk, and an additional 22% formed Type I foci. Treatment of 'initiated' 10T1/2 cells with the tumor promoter 12-O-tetradecanoylphorbol-13-acetate accelerated the formation of transformed foci in the coculture system by reducing the length of the latent period to less than 3 wk. Injection of 10(6) 'initiated' cells/mouse sc into nude mice resulted in the appearance of progressively growing fibrosarcomas after a latent period of 5-7 wk. Dietary supplementation with 4-hydroxyphenyl-retinamide prevented tumor formation; after drug withdrawal, tumors developed in all surviving mice after 6 wk. We believe this cell line possess all characteristics expected of 'initiated' cells. With this new cell line, designated INIT/10T1/2, we can now study the early biochemical changes in growth control mechanisms resulting in neoplastic transformation and the mechanism(s) of chemoprevention of cancer by vitamin A. (Author abstract) (31 Refs)

32. THE PATHOGENESIS OF PLASMA CELL TUMORS.

Hollander VP, Platica M

Res. Inst., Hospital for Joint Diseases, New York, NY, 10035

The Handbook of Cancer Immunology Volume 6: Lymphoid Cell Subpopulations-Structure, Function, and Interactions. Waters H, ed. New York, Garland STPM Press, 314 pp., 1981.

The possibility is examined that common factors are at play in the mineral-oil induced plasma cell tumors (PCT) in BALB/c mice because so many endocrine factors appear to modulate tumorigenesis. The working hypothesis involves bacterial lipopolysaccharide in a transformation step, pristane-induced peritoneal factors in the successful adaptation of nascent tumor cells to the host, and finally, an immunosuppression step which permits rapid growth. Hormones are involved in the earlier steps of plasmacytoma development. (145 Refs)

33. A NEW TUMOR-PROMOTING AGENT, DIHYDROTELEOCIDIN B, MARKEDLY ENHANCES CHEMICALLY INDUCED MALIGNANT CELL TRANSFORMATION.

Hirakawa T, Kakunaga T, Fujiki H, Sugimura T
Lab. Molecular Carcinogenesis, NCI, Bethesda, MD, 20205
Science; 216(4545):527-529 1982

Teleocidin, which was isolated from mycelia of Streptomyces, is a potent tumor promoter in mouse skin. The catalytically hydrogenated compound dihydroteleocidin B markedly enhanced cell transformation induced by 3-methylcholanthrene or ultraviolet radiation. Dihydroteleocidin B was at least 100x more effective in enhancing transformation than 12-O-tetradecanoyl phorbol-13-acetate, the strongest promoter known until now, whereas both promoters showed equal capacities to induce early membrane effects and DNA synthesis. (Author abstract) (24 Refs)

34. INHIBITION OF RESPIRATION BY A PHORBOL ESTER TUMOR PROMOTER IN MURINE CULTURED CELLS.

Backer JM, Boersig MR, Weinstein IB
Div. Environmental Sciences and Cancer Center/Inst. Cancer Res., Columbia Univ., New York, NY, 10032
Biochem Biophys Res Commun; 105(3):855-860 1982

The effect upon mitochondrial function of in vitro exposure of intact murine embryo fibroblasts (C3H 10T1/2) to 12-O-tetradecanoyl phorbol-13-acetate (TPA) was investigated. Nontoxic doses of TPA induced a rapid decrease in mitochondrial respiration in both normal and carcinogen-transformed fibroblasts. Alterations in mitochondrial function may play an important role in both the initiation and tumor promotion phases of chemical carcinogenesis. (18 Refs)

35. MORPHOLOGICAL TRANSFORMATION OF C3H/10T1/2 CL8 CELLS BY PROCARCINOGENS.

Oshiro Y, Balwierz PS
G. D Searle and Co., P.O. Box 5110, Chicago, IL, 60680
Environ Mutagen; 4(2):105-108 1982

Transformation of C3H/10T1/2CL8 cells was attempted using two 3-day periods of exposure to aflatoxin B1 (AFB1), benz(a)anthracene (BAA), 4-nitroquinoline-1-oxide (4NQO), beta-naphthylamine (BNA), and 2-acetylaminofluorene (2AAF) at various concentrations, with replenishment of the medium between the two exposures and during the final 3 days of exposure. Exogenous activation was not used. Transformation was determined according to the criteria of Reznikoff et al. AFB1, BAA, and 4NQO exhibited both Type II and Type III foci sufficiently to indicate detection of morphological transformation. BNA treatment yielded too few Type II foci for a conclusive result, and no Type III foci; 2AAF induced only 1 Type II focus, indicating a negative result. Simply modifying the 10T1/2 transformation method by increasing the exposure from 1 day to 6 days can increase the sensitivity to some procarcinogens that require metabolic activation. (7 Refs)

36. MURINE LEUKEMIA VIRUS-MEDIATED TRANSFORMATION OF A MOUSE EPITHELIAL CELL LINE MMC-E.

Rapp UR, Keski-Oja J
Lab. Viral Carcinogenesis, NCI, Building 560, Room 21-77, Frederick, MD, 21701
Cancer Res; 42(6):2407-2411 1982

Mouse embryo epithelial cells, MMC-E, were malignantly transformed in culture with MuLV derived from C3H/MCA 5 cells chemically induced by 5-iododeoxyuridine. The frequency of transformation was significantly enhanced if infection was followed by treatment with 100 ng of 12-O-tetradecanoylphorbol-13-acetate per ml. The virus-transformed cells retained their high plating efficiency in soft agar in the absence of 12-O-tetradecanoylphorbol-13-acetate and formed neoplasms in nude mice. (Author abstract) (24 Refs)

37. ENHANCED TUMOR GROWTH IN VIVO BY A FACTOR IN HUMAN PLATELETS AND RAT LIVER.

Witkoski E, Kepner N, Leitzel K, Rogers C, Jefferson LS, Lipton A
(c/o Lipton) Div. Oncology, M. S. Hershey Medical Center, Pennsylvania State Univ., Hershey, PA, 17033
Cancer Res; 42(6):2350-2352 1982

Liver cell supernatant and platelet extract can promote the in vivo growth of herpes simplex virus type 2-transformed hamster embryo fibroblast cells. Delineation of necessary growth factors for tumor cells in vivo may open up new strategies to inhibit malignant cell growth. (Author abstract) (15 Refs)

38. PLASMA MEMBRANE CHANGES OF LIVER AND MORRIS HEPATOMA INDUCED BY RETINOL IN RATS.

Buchsel R, Reutter W
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Cancer Res; 42(6):2450-2456 1982

The uptake and binding of po-administered labeled all-trans retinol was studied in vivo in rats bearing nine different types of Morris hepatomas. Radioactivity was found in acid-precipitable and acid-soluble fractions of serum, liver, and the respective tumor. In the different types of Morris hepatomas, the uptake of retinol was found to be decreased. Evidently, the decreased uptake of retinol is a common feature of Morris hepatomas and seems to be related to malignant transformation and not to increased growth. A 67% decrease in the incorporation rate of labeled L-fucose and a simultaneously increased turnover of protein-bound L-fucose were the major alterations of the fucoprotein metabolism in the plasma membrane fraction of the liver induced by high doses of retinol. Protein synthesis in retinol-treated rats was unchanged in liver, hepatoma and serum protein during the 1st hr after pulse. However, 2 hr after the L-methionine pulse, an additional increase of the incorporation rate was observed. Fluorographic analysis of the plasma membrane polypeptides revealed characteristic changes in the labeling pattern after labeling with L-fucose in vivo. This study indicates that the increased hepatic secretory activity after high doses of retinol leads to rapid turnover of incompletely fucosylated glycoproteins of the plasma membrane. The subsequent alterations in the glycosylation pattern as revealed by labeling with L-fucose in vivo are not detectable in the tumor plasma membrane. Therefore, the tumor plasma membrane is not the main target organelle of retinol. Possibly, changes in the host rather than in the tumor itself may be responsible for the anticarcinogenic effect of retinol and the retinoids. (72 Refs)

39. GANGLIOSIDE CHANGES INDUCED BY TUMOR PROMOTERS IN PROMOTABLE JB6 MOUSE EPIDERMAL CELLS: ANTAGONISM BY AN ANTIPROMOTER.

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JNCI; 68(3):469-473 1982

Since cell surface gangliosides have been implicated in the regulation of cell growth and differentiation and since tumor-promoting phorbol esters produce a number of membrane changes, the possibility was investigated that ganglioside changes may play a role in promotion of transformation in JB6 mouse epidermal cells. The studies showed that tumor-promoting but not non-promoting phorbol esters produced decreased precursor incorporation into trisialoganglioside GT and increased incorporation into disialoganglioside GD1b and an unknown ganglioside, Gx. These ganglioside responses to promoters were antagonized by the antipromoter retinoic acid, thus suggesting that alterations in ganglioside levels may be involved in promotion of transformation. (Author abstract) (34 Refs)

40. STUDIES ON MANNOSYL CARRIER FUNCTION OF RETINOL AND RETINOIC ACID IN EPITHELIAL AND MESENCHYMAL TISSUES.

De Luca LM

Differentiation Control Section, NCI, Bethesda, MD

J Am Acad Dermatol; 6(4,part2):611-619 1982

Mannosyllretinylphosphate (MRP) acts as a carrier of mannose, mostly in a direct transfer to protein, in the complex biosynthetic mechanism responsible for glycoprotein assembly in mammalian membranes. Five double bonds seem to be required for this function of MRP. In liver and tracheal tissues from vitamin A-deficient hamsters and rats, retinoic acid (RA) and retinol (ROL) were equally effective in normalizing the in vivo incorporation of mannose into glycoproteins within a short time. RA also reversibly increased the adhesive properties of a spontaneously transformed mouse dermal fibroblast cell line (3T12 cells). A free carboxyl group seemed to be required for this activity of RA. Both RA and ROL enhanced the adhesiveness of 3T12 cells, but only the cellular RA-binding protein (RA-BP) was detected, suggesting that the cellular ROL-binding protein (ROL-BP) may not be a requirement for this activity. The 3T12 cells contained a metabolite of RA (compound X), different from ROL, incorporated into a mannosylretinoidphosphate (MXP). This derivative comprised up to 40% of the total pool of 3H-mannose and 14C-RA derivatives synthesized after 48 hr of labeling. The chromatographic properties of this MXP were identical to those of MRP, but the retinoid in MXP (compound X) differed from both ROL and RA. The results suggested that ROL (in the form of MRP) and RA (in the form of MXP) may function as mannosyl carriers in biologic membranes. (27 Refs)

41. TARGET CELLS INFECTED BY AVIAN ERYTHROBLASTOSIS VIRUS DIFFERENTIATE AND BECOME TRANSFORMED.

Samarut J, Gazzolo L
Rockefeller Univ., New York, NY, 10021
Cell; 28(4):921-929 1982

Transformation in vitro of bone marrow cells by avian erythroblastosis virus (AEV) gives rise to rapidly growing cells of erythroid nature. Target cells of neoplastic transformation by AEV are recruited among the early progenitors of the erythroid lineage, the burst-forming units-erythroid (BFU-E). They express a brain-related antigen at a high level and an immature antigen at a low level. We show that AEV-transformed cells express low levels of the brain antigen and high levels of the immature antigen. Their response to specific factors regulating the erythroid differentiation indicates that they are very sensitive to erythropoietin. Furthermore, cells transformed by a temperature-sensitive mutant of AEV differentiate into hemoglobin-synthesizing cells 4 days after being shifted to the nonpermissive temperature. All these properties are similar to those of late progenitors of the erythroid lineage, the colony-forming units-erythroid (CFU-E). These results indicate that the AEV-transformed cells are blocked in their differentiation at the CFU-E stage. (Author abstract) (36 Refs)

42. HORMONE-DEPENDENT TERMINAL DIFFERENTIATION IN VITRO OF CHICKEN ERYTHROLEUKEMIA CELLS TRANSFORMED BY TS MUTANTS OF AVIAN ERYTHROBLASTOSIS VIRUS.

Beug H, Palmieri S, Freudenstein C, Zentgraf H, Graf T
Inst. Virus Res., German Cancer Res. Center, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany
Cell; 28(4):907-919 1982

Chicken erythroblast cell strains and a cell line transformed by ts mutants of avian erythroblastosis virus (AEV) terminally differentiate when shifted to the nonpermissive temperature (42 C). The differentiated cells resemble mature erythrocytes with respect to morphology and ultrastructure, expression of differentiation-specific cell surface antigens, pattern of protein synthesis and hemoglobin content. Terminal differentiation is dependent on conditions favoring the differentiation of normal erythroid progenitor cells, including an erythropoietin-like factor. Colonies of ts AEV cells grown at 42 C in semisolid medium resemble erythrocyte colonies derived from normal erythroid progenitor cells. The colonies obtained were comparable in size or slightly larger than the late erythroid precursor (CFU-E) colonies. These results suggest that AEV-transformed cells are blocked at a stage of differentiation that is more advanced than that of the uninfected target cells. ts AEV cells are irreversibly committed to terminal differentiation within 20 to 30 hr after shift to 42 C. (Author abstract) (42 Refs)

43. VIABLE POLYOMA VIRUS VARIANT WITH TWO ORIGINS OF DNA REPLICATION.

Magnusson G, Nilsson MG
Medical Nobel Inst., Dept. Biochemistry, Karolinska Inst., S-104 01 Stockholm, Sweden
Virology; 119(1):12-21 1982

A viable evolutionary variant of polyoma virus, ev 1001, produced small clear plaques in assays on mouse 3T3 cells. The kinetics of virus formation during a single infection cycle showed that progeny virus was produced more rapidly than in cells infected by wild-type virus. However, an early cytopathic effect on the infected cells appeared to interrupt the process, since the yield of virus was low. Infection of semipermissive rat cells by ev 1001 virus resulted in unusually high transformation frequencies, particularly at low multiplicities of infection. The biological properties of ev 1001 can all be explained by the effect of a duplication of a 250-base pair segment of the polyoma genome in a region located between the 5'-ends of the early and late genes. The evolutionary variant has two origins of DNA replication, as judged by the high rate of DNA synthesis and strong interference with the formation of wild-type virus in coinfection experiments. The variant ev 1001 also induced mouse cells to synthesize cellular DNA more efficiently than wild-type virus. This effect might result from an increased expression of the viral early genes. (Author abstract) (38 Refs)

44. THE KINETICS OF THE PROTECTIVE EFFECT OF BETA-SITOSTEROL AGAINST MNU-INDUCED COLONIC NEOPLASIA.

Deschner EE, Cohen BI, Raicht RF
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
J Cancer Res Clin Oncol; 103(1):49-54 1982

The effect of dietary supplementation with beta-sitosterol (0.2% of diet) was followed in Fischer rats after both acute and chronic feeding. Compared to controls after 3 and 7 days, the number of epithelial cells per crypt column in both plant sterol fed groups was shifted to lower values; moreover, fewer cells above cell position 12 were engaged in DNA synthesis. Continued feeding of beta-sitosterol for 28 wk revealed the number and position of 3HTdR-labeled cells per crypt column after 1 hr pulse labeling to be similar to that seen in the acute phase. However, differences were more marked after 24 hr showing the max number of labeled cells per column to be at least 25% less than the untreated group and the leading edge of labeled cells moving more slowly up the crypt wall. Rats treated with N-methyl-N-nitrosourea (MNU) intrarectally (8 mg/animal) while simultaneously consuming beta-sitosterol demonstrated a reduction in the size of the proliferative compartment as well as the number of labeled cells per crypt column as compared to rodents receiving just the carcinogen (3.3 and 5.4 mean labeled cells per column, respectively). At this time, MNU-treated rats fed beta-sitosterol had a significantly decreased colonic tumor incidence. This plant sterol which passes through the digestive tract relatively unabsorbed appears to slow colonic epithelial cell proliferation resulting in a reduced expression of neoplastic transformation. (Author abstract) (6 Refs)

45. ROUS SARCOMA VIRUS TRANSFORMED CELLS ARE RESISTANT TO CYCLIC AMP.

Roth CW, Singh T, Pastan I, Gottesman NM
Lab. Molecular Biology, NCI, Building 37, Room 2E24, Bethesda, MD, 20205
J Cell Physiol; 111(1):42-48 1982

Rous sarcoma virus (RSV)-transformed Chinese hamster ovary (CHO) cells were found to differ from spontaneously transformed CHO cells in their sensitivity to growth inhibition or changes in cell shape induced by 8-Br-cyclic AMP (BrcAMP) treatment. RSV-transformed rat (NRK) cells were also observed to have reduced sensitivity to BrcAMP. These results indicate that transformation of CHO and NRK cells by RSV alters the cells in a different manner than spontaneous transformation. (31 Refs)

46. THE PHAGOCYTOSIS AND TRANSFORMING ACTIVITY OF CRYSTALLINE METAL SULFIDE PARTICLES ARE RELATED TO THEIR NEGATIVE SURFACE CHARGE.

Abbracchio MP, Heck JD, Costa M
(c/o Costa) Div. Toxicology, Dept. Pharmacology, Univ. Texas Medical Sch. Houston, P.O. Box 20708, Houston, TX, 77025
Carcinogenesis; 3(2):175-180 1982

Crystalline nickel sulfide (alphaNiS) and cobalt sulfide (CoS2) particles can cause greater cell transformation and cellular toxicity than the respective amorphous metal sulfide particles. Cultured mammalian cells phagocytose the crystalline metal sulfide particles more readily than the amorphous ones. In the case of the nickel sulfides, the crystalline metal sulfide particles had negatively charged surfaces (Zeta potential:-27.012 mV) in contrast to the amorphous particles, which were positively charged (Zeta potential: +9.174 mV). X-ray photoelectron spectroscopy analysis of amorphous and crystalline NiS particles revealed that the outermost surface (1-4 nm) of the two particles had striking differences in Ni/S ratios and in their sulfur oxidation states. Rendering particles' surfaces more negative by reduction with lithium aluminum hydride enhanced their phagocytosis, and in the case of amorphous NiS chemical reduction resulted in an incidence of morphological transformation of Syrian hamster embryo cells comparable to that observed with untreated crystalline alphaNiS. (Author abstract) (17 Refs)

47. ACTIVATION OF NON-EXPRESSED BOVINE PAPILLOMA VIRUS GENOMES BY TUMOUR PROMOTERS.

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Nature; 296(5858):675-677 1982

Following infection of mouse embryo fibroblasts (MEF), bovine papilloma virus type 1 (BPV-1) genome resides in a non-expressed episomal state. After passaging of the BPV-1 infected cells, the viral DNA is eventually lost due to failure to replicate, as shown by hybridization of the viral DNA to a BPV-1 DNA probe according to the Southern method. When BPV-1-infected MEF cells were treated with the tumor promotor 12-O-tetradecanoylphorbol-13-acetate (TPA), considerably more BPV-1 DNA was found after 4 days than in the non-treated cells. Even when TPA was administered to cells in the passage 3 after infection, viral DNA could be detected while none was detectable in non-treated passage 3 cells. Viral DNA was detected at passages 1 and 5 after TPA removal, indicating that BPV-1 DNA continues to replicate in the absence of TPA. TPA also promoted viral transcription. While no viral RNA sequences could be detected in untreated MEF cells one passage after infection, 4 days after TPA treatment of a parallel culture, several species of BPV-1 RNA were found. The same RNA species were detected in BPV-1-induced hamster embryo fibroblasts. Similar results to TPA were obtained with 12-O-retinoylphorbol-13-acetate (RPA). In addition to induction of viral transcripts, TPA induced a transformed phenotype, expressed by an increase in saturation density of the cultures and the ability to grow in low serum medium. While several primate cell lines showed none of these effects, bovine fetal thyroid (BFT) cells did exhibit an enhanced DNA replication and a transient transcription and phenotypic transformation in the presence of TPA and RPA. Tumor promoter-treated MEF and BFT cells may provide a system for studying the amplification and expression of foreign genes inserted into a

BPV-1 vector as well as a screening system for putative tumor-promoting agents. (22 Refs)

48. TUMOR PROMOTERS INCREASE THE SYNTHESIS OF A 32,000-DALTON PROTEIN IN BALB/C 3T3 CELLS.

Hiwasa T, Fujimura S, Sakiyama S
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Proc Natl Acad Sci USA; 79(6,part1):1800-1804 1982

The effect of 12-O-tetradecanoylphorbol 13-acetate (TPA), a potent tumor promoter, on the synthesis of proteins in BALB/c 3T3 mouse fibroblasts has been studied. When [35S]methionine-labeled proteins synthesized after the addition of TPA were analyzed by one- or two-dimensional polyacrylamide gel electrophoresis, the increased synthesis of a 32,000-dalton protein (designated p32) was noted as one of the earliest changes. The synthesis of p32 increased approx two-fold within 2 hr at a promoter concentration of 20 ng/ml. Phorbol 12,13-didecanoate, another potent tumor promoter, showed the same effect as TPA, whereas 4-O-methyl-TPA, which has little promoting activity, did not enhance the synthesis of p32 at the same concentration but did effect a slight increase at 1 ug/ml. p32 differed immunologically from a major excreted protein discovered by Gottesman. The increased rate of the synthesis of p32 was considered to be regulated at the transcriptional level, because the increase in synthesis of p32 was inhibited by actinomycin D, and TPA-treated cells were shown to contain a higher level of translatable mRNA coding for p32 than do control cells. A possible relationship between the increase in p32 synthesis and transformation is discussed. (Author abstract) (49 Refs)

49. MODIFICATION OF BENZO[A]PYRENE-INDUCED TRANSFORMATION OF C3H/10T1/2 CELLS BY PREGNENOLONE-16ALPHA-CARBONITRILE AND DEXAMETHASONE.

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Cancer Lett; 15(3):215-221 1982

The effect of microsomal enzyme inducers, pregnenolone-16alpha-carbonitrile (PCN) and dexamethasone (DEX), on benzo[a]pyrene (BP)-induced transformation of C3H/10T1/2 cells is described. Data for benz[a]anthracene (BA) cytotoxicity and transformation which was used as a control, are presented. PCN increased the toxicity of BP and also increased the BP-induced transformation in a dose-dependent manner. Max enhancement of transformation occurred at 58 uM PCN and was 250% of the BP alone treated culture. DEX caused a dose-dependent reduction in BP-induced cellular transformation. Max reduction (65%) was observed at 23 uM DEX. DEX pretreatment also reduced the cytotoxic effect of BP. DEX treatment alone was not cytotoxic. The simultaneous treatment with DEX did abolish the toxic effect of BP, while PCN did not statistically alter BP toxicity. Both PCN and DEX only slightly induced aryl hydrocarbon hydroxylase (AHH) activity in the cells after a 24-hr treatment. The induction was maximal at approx 0.23 uM for DEX and 2.3 uM for PCN. The induction was much lower than that observed for BA. The greatest difference in metabolism of BP by pretreated C3H/10T1/2 cells occurred at 8-12 hr after the addition of BP. By 24 hr the amount metabolized in control and pretreated cells is nearly equivalent. Results suggest that a correlation between the ability of PCN and DEX to induce AHH activity or BP metabolism to water soluble products and their ability to alter transformation is not entirely consistent. (20 Refs)

50. GENETIC ANALYSIS OF THE ROLE OF CAMP IN MEDIATING EFFECTS OF INTERFERON.

Schneck J, Rager-Zisman B, Rosen OM, Bloom BR
Dept. Microbiology and Immunology, Albert Einstein Coll. Medicine, Bronx, NY, 10461
Proc Natl Acad Sci USA; 79(6,part1):1879-1883 1982

The effects of interferon (IFN) on Fc receptor-mediated phagocytosis, intracellular cAMP levels, antiviral activity, and growth inhibition were analyzed in a cloned macrophage-like cell line, J774.2, and variants derived from it. Purified IFN increased Fc receptor-mediated phagocytosis in J774.2 cells, and in cAMP-responsive nonphagocytic variants but was without effect in cAMP-unresponsive nonphagocytic variants, in adenylate cyclase-deficient variants, and in cAMP-dependent protein kinase-deficient variants. Under conditions in which IFN augmented phagocytosis, it increased intracellular levels of cAMP. Parental cells were highly sensitive to IFN-mediated growth inhibition. In contrast, cAMP-dependent protein kinase-deficient variants were only 1/100th as sensitive to growth inhibition by IFN. All cell lines tested, both responsive and unresponsive to cAMP, were equally protected by IFN against infection with vesicular stomatitis virus, demonstrating that the antiviral state was independent of cAMP. These results indicate that, in transformed macrophages, stimulation of phagocytosis and inhibition of growth by IFN are mediated through intracellular cAMP, whereas the antiviral state induced by IFN is independent of cAMP. (Author abstract) (31 Refs)

51. ROLE OF FIBRONECTIN DEGRADATION PRODUCTS ON CELLULAR TRANSFORMATION.

Barlati S, De Petro G, Vartio T, Vaheri A
Istituto di Genetic Biochimica ed Evoluzionistica CNR, 27100 Pavia, Italy
Protides Biol Fluid Proc Colloq; 29:303-306 1982

The possible association of transformation enhancing factor (TEF) activity with fibronectin (FN) and/or fibrinogen (FG) degradation products [obtained by plasmin digestion of purified human plasma FN (FNdP) and FG] was studied. Plasminolytic fragments of FN but not of FG have potent TEF activity associated with the aggregated fragments of FN but not with the N-terminal of 30 kilodalton fragments carrying the transglutaminase substrate site. The potent TEF activity of FNdP is mimicked by 12-O-tetradecanoylphorbol-13-acetate, widely used as a prototypic tumor promoter. (10 Refs)

52. G-CSF: ITS RELATIONSHIP TO LEUKEMIA DIFFERENTIATION-INDUCING ACTIVITY AND OTHER HEMOPOIETIC REGULATORS.

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J Cell Physiol; Suppl1:53-64 1982

The interrelationship of the various factors produced by WEHI-3 leukemic cells was investigated with particular emphasis on the neutrophil-granulocyte colony-stimulating factor (G-CSF) activity and its relationship to leukemia differentiation-inducing activities induced by endotoxin in mouse and human sera. After stepwise column chromatography of WEHI-3D- conditioned medium (CM), the breakthrough fraction stimulated predominantly neutrophil-granulocyte colony formation, whereas the fraction eluted with 1 M NaCl induced primarily macrophage colony growth. The unseparated but concentrated CM contained significant mast cell growth factors and was a more active source than concanavalin A-stimulated mouse spleen CM. Tumor necrosis factor (TNF) according to the present study, is biochemically and functionally distinct from differentiation-inducing protein (GM-DF). The apparent lack of species specificity of TNF and its selective ability to inhibit proliferation of transformed cells, including WEHI-3B, suggests that acquisition of in vivo sensitivity of TNF may prove an important marker of leukemic transformation. The ability of Corynebacterium parvum plus endotoxin to induce high serum levels of TNF and of GM-DF with similar kinetics points to the importance of synergism studies with various biological response modifiers since TNF inhibits leukemic cell clonal expansion by a direct antiproliferative action, whereas GM-DF inhibits leukemic cell self-renewal by promoting terminal differentiation. (43 Refs)

53. CALCIUM DEPENDENCE OF CHEMICAL CARCINOGEN INDUCED MORPHOLOGICAL TRANSFORMATION OF SYRIAN HAMSTER EMBRYO CELLS.

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Tumor Biology Section, Lab. Biology, NCI, NIH, Bethesda, MD, 20205
Cancer Lett; 15(3):271-279 1982

The levels of extracellular calcium (ECCa) in the cell culture medium were reduced from 1.8 milliM (mM) to 0.2 mM after carcinogen treatment (CT) of Syrian hamster embryo cells. Cell proliferation and frequency of carcinogen induced morphological transformation were examined 6 days after CT to further evaluate the role of ECCa during the early stages of carcinogenesis in mammalian cells. The reduction in transformation may result predominantly from decreased cell proliferation, since the transformation frequency/colony formed in 0.2 mM calcium (Ca) is similar to that in the presence of 1.8 mM Ca. Both cell proliferation and transformation are also decreased if the reduction from 1.8 to 0.2 mM Ca is instituted 1 day after CT. Results in the latter experiment suggest that reduction in the frequency of transformation is greater than the reduction in cell proliferation. If Ca level in the medium is reduced to 0.2 mM commencing 3 days after carcinogen exposure, cell proliferation and transformation are unaffected unless Ca is further reduced to 0.01 mM. The inhibition is due to the reduction in Ca and not to the presence of the chelator [ethylenebis(oxyethylenenitrilo)]-tetraacetic acid in the decalcified serum, as inclusion of the decalcified serum in the regular Dulbecco's medium supports transformation by benzo[a]pyrene, UV irradiation, or n-acetoxyacetylaminofluorene. Morphological transformation is sensitive to reduction in ECCa to 0.01 mM as late as 5 days after CT. (28 Refs)

54. EFFECT OF MOUSE INTERFERON ON CELL TRANSFORMATION AND VIRUS PRODUCTION IN RAT CELLS EXOGENOUSLY INFECTED WITH MOLONEY MURINE SARCOMA AND LEUKEMIA VIRUSES.

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Microbiology and Immunology Unit, Faculty Health Sciences, Ben Gurion Univ. Negev, Beer Sheva, Israel
Int J Cancer; 29(4):471-476 1982

Foci of transformed cells, produced by MSV(124), appeared to result only from the primary infection, since this virus stock yielded a virus-nonproducing infection. On the other hand, the majority of foci scored in MSV/MLV-infected cultures, were generated by multiple secondary infections with the progenies of the primary infection. Mouse interferon (IF) was highly inhibitory for cell transformation by both virus stocks. However, this inhibition was apparent in MSV(124) infected cultures only if IF was added at least 12 hr before infection, whereas in MSV/MLV-infected cultures IF was highly effective even if added 24 hr after infection. The inhibition of focus formation by MSV(124) was irreversible after removal of IF, suggesting that IF inhibited an early step before provirus integration into the host genome. By contrast, in MSV/MLV-infected cultures focus formation was almost completely restored after recovery from the IF effect. Nevertheless, examination of virus production after IF removal proved that in MSV/MLV infection, too IF exerted an inhibitory effect before provirus integration. (Author abstract) (38 Refs)

BIOCHEMICAL AND MOLECULAR BIOLOGICAL STUDIES OF TRANSFORMED PHENOTYPE

55. TEMPERATURE-SENSITIVE CHANGES IN THE STRUCTURE OF GLOBIN CHROMATIN IN LINES OF RED CELL PRECURSORS TRANSFORMED BY TS-AEV.

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Cell; 28(4):931-940 1982

Chicken bone marrow cells infected in vitro with a temperature-sensitive avian erythroblastosis virus fail to produce hemoglobin at 36 C. When the product or products of the transforming gene (erb) are inactivated by a temperature shift to 42 C in culture, several different cloned lines of cells infected with the temperature-sensitive avian erythroblastosis virus begin to make hemoglobin. This shift in phenotype correlates with an increase in hemoglobin mRNA specific to both adult and embryonic alpha and beta globin. The switch is accompanied by the acquisition of DNAase I-hypersensitive sites in one cell line (clone 2); however, a hypothetically more mature line (clone 3) has already acquired globin DNAase-hypersensitive sites but does not express hemoglobin until the temperature shift. Several (but not all) specific restriction sites associated with both the alpha and beta domains become unmethylated after the switch from 36 C to 42 C. The magnitude of these methylation switches is small compared with changes that occur in these genes during normal avian erythropoiesis. The results suggest that changes in chromosomal structure precede transcription and are not a consequence of transcription. Since (presumptive) precursor cloned lines can be established with some, but not all, of the structural properties of active globin chromatin, it is likely that many of these properties can be independently established and are not obligatorily related. (Author abstract) (41 Refs)

56. PROPERTIES OF T ANTIGEN-POSITIVE PHENOTYPIC REVERTANTS ISOLATED FROM SV40-TRANSFORMED RAT AND MOUSE CELLS.

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Microbiol Immunol; 26(1):31-40 1982

T antigen-positive revertants isolated from SV40-transformed rat and mouse cells, which integrate six and two genome equivalents of viral DNA per cell respectively, were tested for tumorigenicity in nude mice and the relationship between tumorigenicity and karyological and growth properties of the cells was investigated. Three phenotypic revertants, R14, R15, R16, were isolated from W-3Y-23 cells. In soft agar medium, W-3Y-23 cells formed large colonies, R16 cells formed slightly smaller colonies, and neither R14 nor R15 formed large colonies. Revertant R14 showed a marked increase in the number of chromosomes to a median value of 130 and no subtetraploid cells were observed in their population. R15 and R16 showed a subtetraploid distribution similar to the parent cell line. W-3Y-23 cells were strongly tumorigenic and all the mice that received either high or low dose developed tumors within a wk. No tumors developed within 11 wk when approx 10(7) 3Y1-B, R14, or R15 cells were injected. R16 cells induced tumors that developed very slowly and became visible 8 wk after inoculation. All the tumors developed at the site of injection. R14, R15, and R16 cell DNA as well as W-3Y-23 DNA were cleaved with EcoRI which cuts the SV40 DNA once, and the DNA fragments containing the viral DNA sequence were analyzed. W-3Y-23 DNA generated seven distinct bands which were identical to those previously detected. Similar patterns were observed with all the revertant DNA; however the second and fourth bands from top of the gel were absent in all revertant DNA. In addition, the smallest band was generated from R14 and R15 DNA. The results indicate that a part of the viral DNA sequence had been deleted in all the revertants, while they still retained at least one complete viral genome. (19 Refs)

57. CHANGES IN PROSTAGLANDIN LEVELS IN CULTURES OF SV40-TRANSFORMED MACROPHAGE CELL LINES IN RELATION TO THEIR PHENOTYPIC EXPRESSION.

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Microbiol Immunol; 26(1):59-66 1982

Prostaglandin (PRG) levels were determined in culture fluids of simian virus 40-transformed cells, line 28-12 and its subline, and the release of PRG by the cells when they are treated with lipopolysaccharide (LPS) and OK-432 (a streptococcal preparation from penicillin-attenuated Streptococcus pyogenes) was investigated. Low levels of PRG were detected in Dulbecco's modified Eagle's medium, and significantly higher levels (4,921 +-140 picog/ml) were detected in heat-inactivated fetal calf serum. 28-12 cells were cultivated for 16 days and the medium was changed every 4 days. A low level of PRG was detected in 4-day culture medium during the growing phase of the cells. When the proportion of phagocytic cells increased during the stationary phase, a decrease in PRG levels was observed. The levels of PRG remained lower than background levels and constant during the culture period when the 28-12 subline isolated by cultivation with cytosine arabinoside (28-12Ara) was cultivated without a change in the medium for 4 days. Non-phagocytic 28-12 cells and phagocytic 28-12Ara cells were cultivated for 24 hr in the presence and absence of LPS (1 ug/ml) and OK-432 (25 ug/ml). The release of PRG by 28-12Ara cells was markedly enhanced, whereas its release by 28-12 cells was not affected. The results indicate the correlation between the phenotypic change from the nonphagocytic to the phagocytic state and a decrease in PRG levels in culture fluids, and that phagocytic cells are responsive to PRG inducers, whereas nonphagocytic cells are not. (27 Refs)

58. ESTABLISHMENT AND CHARACTERIZATION OF HUMAN NEUROBLASTOMA AND GANGLIONEUROBLASTOMA CELL LINES.

Morrison LJ, Cochran AJ, Gibson AA, Willoughby ML, More IA
Dept. Pathology and Surgery, Univ. California Los Angeles Center for Health Sciences, Los Angeles, CA, 90024
Br J Cancer; 45(4):531-542 1982

The establishment in culture and characterization of four human neuroblastoma (NB) cell lines and one human ganglioneuroblastoma cell line are described. Each cell line fulfilled at least two of four criteria for malignant or transformed cells: viz, subcultured more than 70x, high saturation density with absence of contact inhibition, population-doubling time within a range of 10-40 hr, and tumor formation in nu/nu mice. Each cell line also fulfilled at least two of three criteria for neuroblastoma cells: viz, humoral and cell-mediated immune reactivity toward NB-associated cell-surface antigen, intracellular storage and extra-cellular secretion of catecholamines, and characteristic neuroblast and ganglion-cell morphology. (Author abstract) (22 Refs)

59. PURIFICATION OF GLYCOPROTEIN FROM 'CONDITIONED MEDIUM' OF SPONTANEOUSLY MALIGNANT TRANSFORMED FIBROBLAST CELLS; CELL-SPREADING EFFECT OF THIS GLYCOPROTEIN ON SO-CALLED RETICULUM CELLS CULTURED IN SERUM-FREE MEDIUM.

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Dept. Pathology, Faculty Medicine, Kyoto Univ., Kyoto, Japan
Cell Mol Biol; 27(6):709-717 1981

Mouse fibroblast cells (m cells) and so-called reticulum cells (MR cells and SP cells) transformed into malignant cells in vitro, were transferred to a serum-free culture medium, and the morphological and functional differences of these two kinds of cells were studied. We found that the fibroblast cells produce a unique glycoprotein which has the biological function of inducing cell-spreading of so-called reticulum cells on the substratum in the serum-free culture medium. This glycoprotein was purified from the conditioned medium of the transformed fibroblast cells. The mol wt of this protein is about 230-250 x 10(3) daltons. The so-called reticulum cells themselves do not produce detectable amounts of this protein. Specific antiserum against this glycoprotein shows a single precipitation line against not only this glycoprotein, but also against serum protein. This antiserum inhibits the cell-spreading inducing activity of this glycoprotein in vitro. Immunofluorescent microscopy shows that this glycoprotein exists on the cell surface and in the cytoplasm of normal and some transformed fibroblast cells. Undifferentiated fibrosarcoma cells, however, do not produce this glycoprotein in vitro. (Author abstract) (24 Refs)

60. INTRACELLULAR TRANSPORT OF SV40 LARGE TUMOR ANTIGEN: A MUTATION WHICH ABOLISHES MIGRATION TO THE NUCLEUS DOES NOT PREVENT ASSOCIATION WITH THE CELL SURFACE.

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Virology; 119(1):169-184 1982

The cT mutation of PARA, an SV40-adenovirus 7 hybrid virus, abolishes the transport of SV40 T-antigen (T-ag) to the nucleus and results in the accumulation of T-ag in the cytoplasm of infected and transformed cells. The effect of the cT mutation on the association of T-ag with the cell surface was examined in PARA(cT)-infected monkey cells. Surface-associated T-ag was detected by immunofluorescence, lactoperoxidase-catalyzed cell-surface iodination, and cellular fractionation. Surface-associated T-ag was more readily labeled by cell-surface iodination with PARA(cT)-infected cells than with SV40 and wild-type PARA [PARA(nT)]-infected cells. Control experiments eliminated the possibility that the enhanced detection of T-ag in PARA(cT)-infected cells was due to the labeling of intracellular T-ag by lactoperoxidase or to T-ag leaking from dead cells and adhering to the cell surface. The elevated level of surface-associated T-ag in PARA(cT)-infected cells was confirmed by metabolic labeling and cellular fractionation, indicating that the increased iodination of surface-associated T-ag was due to a greater number of T-ag polypeptides on the surface rather than a greater exposure of tyrosine residues. Pulse-chase experiments demonstrated that the elevated level of surface-associated T-ag in PARA(cT)-infected cells was not due to a prolonged stability of surface-associated T-ag. The cT mutation provides a useful tool for studies of mechanisms governing intracellular protein transport. (Author abstract) (47 Refs)

61. NONHISTONE PROTEINS OF RAT LIVER TRANSFORMED BY NITROSODIETHYLAMINE.

Seits IF, Glebov AV
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Vopr Onkol; 28(1):42-46 1982

Qualitative and quantitative content of nonhistone chromosomal proteins (NHP) from normal and nitrosodiethylamine-transformed rat liver was studied. An increase in the protein/DNA ratio in tumor chromatin, as compared with that of normal tissue, was established. NHP were extracted from the chromatin with 0.4 N N2SO4 and fractionated with two-dimensional polyacrylamide gel electrophoresis. Coomassie staining revealed more than 80 fractions with mol wt ranging 20-150 th. Some quantitative and qualitative differences in the patterns of NHP from normal and neoplastic tissues were observed. A conclusion is drawn that these differences may be related to structural and/or enzymatic components of NHP. (Author abstract) (17 Refs) (In RUS)

CELL SURFACE PHENOMENA OF TRANSFORMATION

62. TRANSCRIPTION OF THE HEPATITIS B SURFACE ANTIGEN GENE IN MOUSE CELLS TRANSFORMED WITH CLONED VIRAL DNA.

Pourcel C, Louise A, Gervais M, Chenciner N, Dubois MF, Tiollais P
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J Virol; 42(1):100-105 1982

Mouse L cells transformed with recombinant plasmids carrying hepatitis B virus (HBV) DNA fragments were used to study the transcription of the viral surface antigen gene (gene S). An HBV-specific, polyadenylated, 2.3-kilobase RNA was mapped on the HBV genome. This RNA hybridized with approx 75% of the genome and excluded the region of the HBV core antigen gene (gene C). The 2.3-kilobase RNA species was present only in cell lines that produced hepatitis B surface antigen. An HBV-specific 2.3-kilobase RNA was also detected in human hepatoma cell line PLC/PRF/5 which produced hepatitis B surface antigen. A study of gene S expression in the transformed mouse L cells allowed us to localize the regions of initiation and termination of gene S transcription. Our results strongly suggest that the 2.3-kilobase RNA molecule is the mRNA of the major polypeptide of the envelope, which carries the viral surface antigen determinants. (Author abstract) (21 Refs)

63. DETECTION OF HERPES SIMPLEX VIRUS TYPE 2 GLYCOPROTEINS EXPRESSED IN VIRUS-TRANSFORMED RAT CELLS.

Lewis JG, Kucera LS, Eberle R, Courtney RJ
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J Virol; 42(1):275-282 1982

Rat embryo fibroblasts transformed by herpes simplex virus Type 2 (HSV-2) were assayed for the expression of certain virus-specific glycoproteins on the surface membranes. Monospecific antisera to HSV-2-specific glycoproteins, designated gAgB, gC, and gX, were used in membrane immunofluorescence studies with HSV-2-transformed cell lines tREF-G-1, tREF-G-2, and a tumor-derived rat fibrosarcoma cell line produced in syngeneic rats inoculated with tREF-G-1 cells. Analysis of the three HSV-2-transformed cell lines showed that antisera to the gAgB and gX glycoproteins were reactive with these cells. In contrast, no significant reactivity was observed when anti-gC serum was reacted with the HSV-2-transformed cell lines. All three antiglycoprotein sera reacted positively with rat cells productively infected with HSV-2. Additionally, the HSV-2-transformed and tumor-derived cell lines showed positive internal immunofluorescence after reaction with antiserum to an early, nonstructural viral protein designated VP143 (mol wt, 143,000). Infectivity of HSV-2 in standard plaque assays was neutralized by hyperimmune rat antisera to tREF-G-2 or rat fibrosarcoma cells and to HSV-2 virions and by sera from rats bearing the fibrosarcoma. Adsorption of rat anti-HSV-2 virions serum with tREF-G-2 or rat fibrosarcoma cells reduced neutralizing activity to 10 and 12%, respectively, compared with 90% neutralization by antiserum adsorbed with nontransformed rat embryo fibroblast cells and 100% neutralization with unadsorbed antiserum. In summary, HSV-2-transformed rat cells retained and expressed genetic information necessary for the production of HSV-2 glycoproteins and a nonstructural protein after high passage in tissue culture or in the syngeneic host. (Author abstract) (28 Refs)

64. DISSECTION OF THE ANTIGENIC DETERMINANTS EXPRESSED ON THE CELL SURFACE OF RSV-TRANSFORMED FIBROBLASTS BY MONOCLONAL ANTIBODIES.

Ferracini R, Prat M, Comoglio PM
Univ. Trieste, Sch. Medicine, Trieste, Italy
Int J Cancer; 29(4):477-481 1982

Fusion of P3/X63-Ag8 mouse myeloma cells with splenocytes obtained from mice hyperimmunized with a BHK hamster fibroblast line transformed by an env-strain of Rous sarcoma virus (RSV) resulted in the production of antibody-secreting hybridomas. Seven hybrid clones secreted antibodies binding to RSV-transformed BHK fibroblasts but not to the parental control non-transformed line. The antibodies produced by three of these clones did identify antigenic determinants expressed also on BHK cells transformed by SV40. The antibodies produced by four other clones reacted specifically with cells transformed by RSV but not with cells productively infected by the transformation-defective Rous-associated virus-I; one of these reacted with RSV-transformed hamster cells only, three others identified antigenic determinants common to RSV-transformed cells of different animal species. These data give further support to the idea that RSV-transformed cells express a cell-surface antigen, specific for transformation, the expression of which is controlled by the transforming src gene, and that the specificities carried on it follow a complex pattern, arising from the interaction between antigenic determinants of cellular and viral origin. (Author abstract) (49 Refs)

65. TRANSFERRIN RECEPTORS IN TRANSFORMATION AND DIFFERENTIATION.

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Protides Biol Fluid Proc Colloq; 29:451-454 1981

Human promyelocytic leukemia HL-60 cells, Burkitt's lymphoma Daudi cells, and myelogenous leukemia K562 cells were grown with 1.25% dimethylsulfoxide (DMSO), 0.1% sodium n-butyrate (SnB), or 1 x 10(-6) retinoic acid (RA) for 4 days at 37 C, and transferrin receptors and growth were examined. HL-60 cells originally consisted of myeloblasts and promyelocytes and differentiated to metamyelocytes and banded neutrophils following induction; Daudi and K562 cells were unchanged. The indirect immunofluorescence test revealed that all three cell lines were strongly reactive for transferrin receptors, but HL-60 cells were weakly reactive after culture with DMSO, SnB, or RA; Daudi and K562 cells remained strongly reactive. Growth of HL-60 cells was strongly inhibited by all three agents, Daudi cells by SnB, and K562 cells by RA; K562 cells were barely affected by SnB. These findings indicate a role for transferrin receptors in differentiation and transformation: loss of receptor activity may be interpreted as being an index of change from immature to mature or from malignant to normal. (18 Refs)

66. MONOCLONAL ANTIBODY AGAINST EBV-ASSOCIATED TRANSFORMATION ANTIGEN DETECTED IN VITRO AND IN VIVO.

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Protides Biol Fluid Proc Colloq; 29:739-742 1982

Transformation antigens on the surface of in vitro Epstein-Barr virus (EBV)-transformed B lymphocytes were defined by producing specific monoclonal antibodies. A hybridoma (17D6) was cloned and analyzed for its binding properties to a variety of EBV-positive and -negative B cell lines. The antibody reacted strongly with all of the EBV-positive lines and weakly with the EBV-negative lines. Similarly, a panel of EBV-negative cell lines from a variety of sources reacted only weakly with the 17D6 antibody. When a whole panel of EBV-infected cells from sources other than in vitro infection were tested, all the cell lines containing EBV were as positive as in vitro infected cells, including one cell line derived by spontaneous outgrowth from an EBV-positive individual and one from co-cultivation of normal lymphocytes from a seronegative individual with a nasopharyngeal carcinoma. Burkitt's lymphoma tumor cells reacted only weakly with the 17D6 antibody due to their relatively low levels of the antigen. 17D6-positive cells also were detected in the peripheral blood of infectious mononucleosis (IM) patients. 17D6-positive cells could be detected in the peripheral blood of a patient with chronic EBV infection at higher levels than in patients with acute IM. After recovery, no 17D6-positive cells could be detected. Radioimmunoprecipitation studies suggested that the 17D6 antibody recognizes a polypeptide of 40,000 mol wt. The results indicated that the 17D6 antibody recognizes an EBV-associated transformation antigen on the surface of in vitro and in vivo infected cells. (4 Refs)

67. CHANGES IN PHOSPHOLIPID POLAR HEAD GROUP TURNOVER IN SV40-TRANSFORMED HAMSTER FIBROBLASTS.

Maziere C, Maziere JC, Mora L, Polonovski J

Laboratoire de Chimie Biologique, C.H.U. Saint-Antoine, 27, rue Chaligny, 75012 Paris, France

FEBS Lett; 139(2):217-220 1982

The effect of viral transformation on turnover of phospholipid polar head groups was studied in vitro in hamster fibroblasts. Cell cultures of SVEHSVi hamster fibroblasts transformed by simian virus 40 (SV40) and cultures of nontransformed EHB hamster fibroblasts were labeled with 0.1 uCi/ml [U-14C]inositol, 0.5 uCi/ml [methyl-14C]choline, or 0.5 or 5 uCi/ml [2-14C]ethanolamine. Phospholipids from cell suspensions were separated by chromatography using chloroform/methanol solvent. Transformed cells incorporated inositol into phosphatidylinositol (PI) approx 2x as rapidly as nontransformed cells. Incorporation of ethanolamine into phosphatidylcholine (PC) and phosphatidylethanolamine (PE) was increased by a similar amount in transformed cells. Incorporation of choline into PC and sphingomyelin (SM) was decreased in transformed cells compared with nontransformed cells. Labeling of SM was delayed compared with labeling of PC. Only 1% of labeled ethanolamine was recovered in PC, indicating that not all PE was transmethylated into PC. Results indicate that transformed cells have a more rapid turnover of phospholipid polar head groups than do nontransformed cells. The significance of the turnover is uncertain, but may be related to cellular adhesive properties. (26 Refs)

MORPHOLOGICAL AND OTHER BIOLOGICAL ASPECTS OF ONCOGENIC TRANSFORMATION

68. GENETIC MODEL OF CELL DEATH: HYPOTHESIS AND APPLICATIONS (TRANSFORMATION, CARCINOGENESIS, AGING).

Umanskii SR

Inst. Biological Physics, Pushchino, USSR

Usp Sovrem Biol; 93(1):139-148 1982

The mechanisms of the cell death are discussed, with special emphasis on the role of DNA degradation in neoplastic cell transformation and aging. It was suggested that the elimination of cells carrying the oncogenic mutation is associated with the functioning of the genetical program of cell death and that the reproduction of the mutant cells is possible only after modification of the program. (48 Refs) (In RUS)

69. SOLUBLE CYTOSTATIC FACTOR(S) RELEASED FROM HUMAN MONOCYTES. I. PRODUCTION AND EFFECT ON NORMAL AND TRANSFORMED HUMAN TARGET CELLS.

Hammerstrom J
Section Haematology and Immunology, Dept. Medicine, Trondheim Regional Hosp., N-7000 Trondheim, Norway
Scand J Immunol; 15(3):311-318 1982

Human monocytes activated with lymphokines after 3-7 days of in vitro maturation released stable cytostatic factor(s) (CF), as determined by reduction of [methyl-3H]thymidine incorporation and cell counts in target cell cultures. Lipopolysaccharide from Escherichia coli slightly enhanced the release of CF. The CF release was greatest at an intermediate stage of the in vitro monocyte maturation to large, macrophage-like cells. Three transformed human cell lines (NHIK 3025, K-562, and U-20S) and normal skin fibroblasts were consistently inhibited by CF. Normal human mesothelial cells were variably affected while normal human lymphocytes proliferating in response to allogeneic cells in mixed lymphocyte culture were not inhibited. Further analysis of CF may disclose one of the mechanisms whereby human monocytes and macrophages inhibit growth of human tumor cells. (Author abstract) (34 Refs)

70. NOVEL LOCALIZATION OF PP60SRC IN ROUS SARCOMA VIRUS-TRANSFORMED RAT AND GOAT CELLS AND IN CHICKEN CELLS TRANSFORMED BY VIRUSES RESCUED FROM THESE MAMMALIAN CELLS.

Garber EA, Krueger JG, Goldberg AR
Rockefeller Univ., New York, NY, 10021
Virology; 118(2):419-429 1982

We have investigated by indirect immunofluorescence and subcellular fractionation the intracellular location of pp60src in RSV-transformed mammalian cells and in CEF cells transformed by virus rescued from these cells. Two independently derived cell lines were examined: RR1022 cells isolated from an in vivo sarcoma induced in an Amsterdam rat by infection with SR-RSV-D; and Pcl, cells isolated from a soft agar colony of normal goat skin fibroblasts transformed in vitro by SR-RSV-D. Transforming viruses (RSV-RR and RSV-Pcl) were rescued from RR1022 and Pcl cells by fusion with CEF cells. Immunofluorescence microscopy showed association of pp60src with the nuclear envelope and the juxtanuclear reticular membranes in the transformed mammalian cells and in CEF cells transformed by the rescued viruses, in contrast to the plasma membrane localization of pp60src seen in SR-RSV-transformed CEF cells. Results of subcellular fractionation by differential centrifugation and fractionation of particulate fractions by equilibrium centrifugation in discontinuous sucrose gradients were in agreement with the differences in pp60src distribution observed by immunofluorescence microscopy. Although the mammalian cell lines were independently derived, pp60srcs isolated from RR1022 and Pcl cells both lacked amino-terminal 21-and 18-kilodalton [35S]methionine S aureus V8 protease peptides found in SR-RSV-D pp60src. Proteolytic peptides identical to those of pp60src from the mammalian cells were obtained from pp60src proteins isolated from rescued virus-transformed CEF cells, suggesting that the alteration in the amino-terminal half of the src protein represents a stable change, and that an alteration in the primary structure of pp60src is responsible for the altered intracellular membrane localization of pp60src in these cells. (Author abstract) (25 Refs)

71. ACTIN MUTATIONS IN A HUMAN FIBROBLAST MODEL FOR CARCINOGENESIS.

Leavitt J, Goldman D, Merril C, Kakunaga T
Linus Pauling Inst. Science and Medicine, Palo Alto, CA, 94306
Clin Chem; 28(4,part2):850-860 1982

We assessed the modulation of gene expression accompanying neoplastic transformation by computerized microdensitometry of autoradiographic patterns of [35S]methionine-labeled polypeptides separated by two-dimensional polyacrylamide gel electrophoresis. Nearly 1,000 polypeptide species of parent diploid human fibroblasts (KD strain) were compared. We found that the neoplastic HUT-14 fibroblasts express a mutation in one of the two functional beta-actin genes. In addition, of the 700 more-abundant polypeptides measured, 13 were lost and 14 new ones gained after this neoplastic transformation. We estimate that although 2% or fewer of the genes expressing abundant polypeptides were either activated or shut off, at least 32% were modulated quantitatively. A substrain of HUT-14-HUT-14T - shows increased tumorigenicity, producing larger, faster-growing fibrosarcomas in the nude mouse than does the present parent HUT-14 strain, and with fewer inoculated cells. This increase in tumorigenicity is accompanied by three subsequent changes in the mutant beta-actin polypeptide expression. A more variant mutant actin species is synthesized in HUT-14T, which differs from the original mutant polypeptide by (i) one additional negative net charge, (ii) a short half-life in the cell, (iii) a greatly diminished ability to incorporate into the detergent-resistant cytoskeleton, (iv) a decrease in affinity for deoxyribonuclease I (EC 3.1.21.1), and (v) a faster rate of synthesis. Our results suggest that a second-site mutation in the mutant beta-actin of HUT-14 was selected for during a subcloning step in the presence of 6-thioguanine before derivation of the HUT-14T substrain. This apparent mutation and two subsequent defective beta-actin expressions are accompanied by incremental increases of malignant potential. (Author abstract) (21 Refs)

72. ULTRASTRUCTURAL DIFFERENCES BETWEEN CONTROL AND NITROSOMETHYLUREA-TRANSFORMED CELLS OF RAT HEPATOCYTE ORIGIN.

Kaplan AE, Yamaguchi MK, Tralka TS, Hanna CH
NIH, Building 37-3B27, Bethesda, MD, 20208
Exp Cell Res; 138(2):251-260 1982

Ultrastructural comparisons identify significant differences between a control cell, TRL 12-13, and a nitrosomethylurea-transformed cell line, NMU-3, which secretes lactic acid in vitro and produces carcinomas in vivo. Both cell lines were established from rat hepatocytes. The NMU-3 cells show a marked reduction in mitochondria, both at confluence and at 48 hr post-confluence. This deficiency supports previous biochemical findings of altered bioenergetic pathways in the NMU-3 cells, leading to increased output of lactic acid. In addition to deficiencies in mitochondria, the NMU-3 cells show a marked reduction in other membranous structures, including rough endoplasmic reticulum, Golgi apparatus, pinocytotic and coated vesicles. Polyribosome distribution at confluence and 48 hr later suggests that the transformed cells continue to synthesize intracellular protein, whereas the control cells appear to secrete protein for export at this time. (Author abstract) (29 Refs)

73. LACK OF TROPOMYOSIN CORRELATES WITH THE ABSENCE OF STRESS FIBERS IN TRANSFORMED RAT KIDNEY CELLS.

Leonardi CL, Warren RH, Rubin RW
Dept. Anatomy and Cell Biology, Univ. Miami Sch. Medicine, P.O. Box 016960, Miami, FL, 33101
Biochim Biophys Acta; 720(2):154-162 1982

We have utilized epithelial rat kidney cells and their Kirsten viral transformant (442) to examine the role of actin-binding proteins in cellular morphogenesis. Normal rat kidney cells are well spread while the transformed cells are more spherical, poorly adherent, and lack actin stress fibers. By immunofluorescence, anti-tropomyosin prominently stains normal rat kidney cell stress fibers while only a weak, nonspecific fluorescence is observed in 442 cells. Using two-dimensional gel electrophoresis, tropomyosin can be detected in normal rat kidney cell homogenates. The tropomyosin subunits are enriched in Triton-extracted filamentous normal rat kidney cell models, and in extracts of normal rat kidney cell homogenate produced by using a rapid myosin affinity technique to isolate actin and actin-associated proteins. The identity of the tropomyosin subunits has been confirmed by electrophoretic mobility, lack of proline, and the peptide map generated by limited proteolysis. None of these techniques have detected tropomyosin in the corresponding 442 preparations. Our results suggest that transformation of normal rat kidney cells has led to an overall reduction in tropomyosin content. This may be related to the inability of 442 cells to organize filamentous actin stress fibers. (Author abstract) (37 Refs)

ASSAYS OF ONCOGENIC TRANSFORMATION

74. ANALYSIS OF N-ACETOXY-N-2-ACETYLAMINOFLUORENE-INDUCED FRAME-SHIFTS IN PBR322.

Yoon K, Shelegedin VN, Kallenbach NR
Center Oral Health Res., Sch. Dental Medicine, Univ. Pennsylvania, Philadelphia, PA, 19104
Mutat Res; 93(2):273-283 1982

A simple system is described which can be used to study directly the sequence change and cellular functions involved in frame-shift mutagenesis by covalently reactive mutagen. Positive and negative alterations in the number of base pairs of tetracycline resistant gene of pBR322, were created by cutting with Sal restriction enzyme followed by either removal with nuclease Sl or extension with reverse transcriptase, and reclosing by a 'blunt-ended' joining reaction catalyzed by T4 DNA ligase. Mutagenesis in vitro by exposure to N-acetoxy-N-2-acetylaminofluorene (AAAF) was used to cause reversion of frame-shifted plasmid molecules. Transformation of AAAF-reacted frame-shift plasmid DNA into Escherichia coli strains AB1157, AB1886, and AB2463 was performed, and a number of revertants (ApRTcR) not represented in unreacted controls were generated. Differential inactivation of the AP gene was observed among the E coli strains. The system used here is suitable for any chemicals that bind covalently to DNA. (25 Refs)

75. UTILIZATION OF CELL TRANSFORMATION TESTS IN THE DETECTION OF CHEMICAL CARCINOGENS.

Elias Z, Cavelier C
Institut National de Recherche, Centre de Recherche de Nancy, avenue de Bourgogne, F-54500 Vandoeuvre-les-Nancy, France
Bull Cancer (Paris); 69(1):33-57 1982

A great variety of practical short term tests for detecting potential carcinogenic chemicals have been proposed over the last 10 yr. Tests based on the cellular transformation of mammalian cells in culture are included in this group. After a brief review of the different characteristics of this transformation, the principal cell systems, the methods used and the results obtained by authors who developed and/or use these tests, are presented. It seems justified to include the simplest and most reliable of these tests in the battery of screening tests for the research of potential carcinogenic properties of chemicals. The present orientation of research, likely to lead to more discriminating tests, is discussed. (Author abstract) (220 Refs) (In FRE)

GENERAL REVIEWS AND OTHER RELATED STUDIES

76. GENETIC INTERACTIONS BETWEEN TUMOR VIRUSES AND HOST CELLS.

Rowe WP
Lab. Viral Diseases, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20205
Cancer; 49(10):1958-1962 1982

Accomplishments in the field of tumor virology over the past 25 yr are reviewed. The list of viruses known to cause tumors in nature or in laboratory systems has expanded greatly. The oncogenic viruses include retroviruses, herpesviruses, papovaviruses. Dramatic changes have taken place in the study of the genetic interactions between tumor viruses and virus-transformed cells, in searches for virus causation of tumors, and for a genetic and biochemical basis of malignant transformation. Polyoma viruses, adenoviruses, and retroviruses analyzed in mouse or hamster systems are discussed in relation to tumorigenesis. Infectious virus need not be present for tumor induction. Discoveries related to genetic interactions between viral and host cell genes in retrovirus leukemogenesis include the following: viruses produced directly from the inherited endogenous retroviral genes in the mouse are not tumorigenic; during the course of spreading infection, genetic recombinants arise between genomes of the infectious virus and the defective viral genes in the chromosomes of the host; a similar type of recombination can take place between infectious retroviruses and cellular genetic information; in B-lymphocytes transformed by avian retrovirus, only a piece of the virus genome may remain, analogous to the defective genome insertions seen with DNA tumor viruses. Other aspects of tumor virus DNA-host cellular DNA interactions are discussed. (49 Refs)

77. HUMAN PAPILLOMAVIRUS AND ONCOGENESIS.

Jablonska S
Dermatologische Klinik, Koszykowa 82 A, P-02-008 Warszawa, Poland
Z Hautkr; 57(8):551-552,555-560,563,566 1982

Human papillomaviruses (PV) and oncogenesis were discussed, and the following aspects were included: oncogenic properties of animal PV, carcinomas and human PV (PV of larynx in children, genital warts, cervical dysplasia, Bowen's disease, epidermodysplasia verruciformis (EV), the EV induced by human PV-3 and PV-5, cellular immunity (CI), specific CI, and specific humoral immunity), and genetics (importance of determination of types of human PV). (72 Refs) (In GER)

78. CARCINOGENESIS AND CURRENT HYPOTHESIS ON THE TUMOR-HOST INTERACTIONS.

Neiman IM
No affiliation given
Patol Fiziol Eksp Ter; (2):63-70 1981

Current theories of cancer etiology are reviewed with special emphasis on the role of tumor-host interactions and genetic predisposition of the host. It was suggested that exogenous factors (chronic inflammations, chemical and physical carcinogens, oncogenic viruses) can induce the precancerous conditions. Cancer development requires specific malignant transformation, which can take place only in tissues with genetic predisposition. (27 Refs) (In RUS)

79. CHEMICALS, CANCER, AND CYTOCHROME P-450.

Alexander LS, Goff HM
Univ. Iowa, Iowa City, IA, 52242
J Chem Educ; 59(3):179-182 1982

Cytochrome P450 (P450) and related monooxygenases mediate a variety of complex chemical reactions, including the processing of many foreign chemical substances in the circulation. Nearly all putative carcinogens (except for the nitrosamides and a few alkylating agents) require enzymatic activation before they can induce neoplastic transformation of normal cells. The ultimate carcinogen is an electrophile, which covalently binds to DNA, RNA, protein chains, and/or other molecules of importance to cellular reproduction. P450 is often involved in the involved in the metabolic activation of carcinogens. Available evidence on the role of P450 in detoxification and carcinogen activation, its hypothetical reaction cycle with substrates, and the important chemical models used in delineate its active site structure are discussed. (32 Refs)

80. PRINCIPLES OF CANCER BIOLOGY: ETIOLOGY AND PREVENTION OF CANCER.

Upton AC

Dept. Environmental Medicine, New York Univ. Medical Center, New York, NY

Cancer - Principles and Practice of Oncology. DeVita VT, Hellman S, and Rosenberg SA, ed. Philadelphia, Lippincott, 1926 pp., 1982.

Somatic mutation, aberrant differentiation, virus activation, and cell selection form the basis of contemporary theories of carcinogenesis. None of these theories accounts for all of the observed phenomena of neoplasia. Both initiating and promoting factors seem to be required for chemical carcinogenesis in humans. The development of sound safety standards and codes of practice are the best means of risk avoidance, but the development of these standards has often lagged behind the demonstration of carcinogenicity. The problem has been complicated by uncertainty and controversy about the criteria for the determination of the carcinogenicity of a given agent, and also for assessing the magnitude of the risk occurring in exposed populations. Workable interim approaches to the resolution of these problems have been developed. (194 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. TOXICITY AND METABOLISM OF ACRYLONITRILE.
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Zaklad Metabolizmu Substancji Toksycznych, Instytut Medycyny Pracy, ul. Teresy 8, 90-950 Lodz, Poland
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2. A REVIEW OF THE GENOTOXICITY OF FOOD, DRUG AND COSMETIC COLOURS AND OTHER AZO, TRIPHENYLMETHANE AND XANTHENE DYES.
Combes RD, Haveland-Smith RB
Dept. Biological Sciences, Portsmouth Polytechnic, King Henry I St., Portsmouth, PO1 2DY, Hants, England
Mutat Res; 98(2):101-248 1982

3. CARCINOGENICITY OF AIRBORNE FINE PARTICULATE BENZO(A)PYRENE: AN APPRAISAL OF THE EVIDENCE AND THE NEED FOR CONTROL.
Perera F
Natl. Resources Defense Council, Inc., 122 East 42nd St., New York, NY, 10168
Environ Health Perspect; 42:163-185 1981

4. TOXICOLOGY OF N-NITROSO COMPOUNDS.
Coulston F, Olajos EJ
Albany Medical Coll., Albany, NY, 12208
Ecotoxicol Environ Saf; 6(1):89-96 1982

5. CRITICAL REVIEW OF THE MUTAGENIC AND OTHER GENOTOXIC EFFECTS OF DIRECT COAL LIQUEFACTION.
Kimball RF, Manro NB
Oak Ridge Natl. Lab., Oak Ridge, TN
Critical Review of the Mutagenic and Other Genotoxic Effects of Direct Coal Liquefaction. Available from National Technical Information Service, Springfield, VA, as DE81027859:, 216 pp., 1981.

6. CARCINOGENICITY AND ITS EFFECT ON MEDICINAL RESEARCH PROGRAMS IN THE USA.
Van Ryzin RJ
Pharmaceutical Res. and Development, Sandoz, Inc., East Hanover, NJ, 07936
Med Res Rev; 2(2):153-166 1982

7. ANTIPROTOZOAL DRUGS (SIDE EFFECTS).
Nir I
Dept. Pharmacology and Experimental Therapeutics, The Hebrew Univ., Hadassah Medical Sch., Jerusalem, Israel
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8. DRUGS USED IN TUBERCULOSIS AND LEPROSY (SIDE EFFECTS).
Elis J
Inst. Pharmacology, Czechoslovak Acad. Sciences, Albertov 4, Prague 2, Czechoslovakia
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9. SEX HORMONES AND RELATED COMPOUNDS, INCLUDING ORAL CONTRACEPTIVES.
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RADIATION CARCINOGENESIS

10. NEPTUNIUM - THE NEGLECTED ACTINIDE: A REVIEW OF THE BIOLOGICAL AND ENVIRONMENTAL LITERATURE.
Thompson RC
Biology Dept., Pacific Northwest Lab., Richland, WA, 99352
Radiat Res; 90(1):1-32 1982

11. CARCINOGENIC EFFECT OF RADIOACTIVE PRODUCTS.
Vasilenko IIa
No affiliation given
Vopr Onkol; 28(1):76-83 1982
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DIETARY FACTORS IN CARCINOGENESIS

12. FIBRES, NUTRITION AND THE GUT.
Schrijver M, Tytgat GN
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Neth J Med; 25(2):49-55 1982

13. DIETARY FIBER AND DISEASE.
Kritchevsky D
Wistar Inst. Anatomy and Biology, Philadelphia, PA
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14. ASSESSING HUMAN EPIDEMIOLOGIC DATA ON DIET AS AN ETIOLOGIC FACTOR IN CANCER DEVELOPMENT.
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15. NUTRITION AND CANCER: MECHANISMS OF GENOTOXIC AND EPIGENETIC CARCINOGENS IN NUTRITIONAL CARCINOGENESIS.
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ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

17. SKIN CANCER: OCCUPATIONAL CAUSES.
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18. OCCUPATIONAL AND ENVIRONMENTAL HEALTH PROBLEMS OF THE DEVELOPING OIL SHALE INDUSTRY: A REVIEW.
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Am J Industr Med; 2(3):247-260 1981

19. POLYCYCLIC AROMATIC HYDROCARBONS IN THE OCCUPATIONAL ENVIRONMENT: WITH SPECIAL REFERENCE TO BENZO[A]PYRENE MEASUREMENTS IN SWEDISH INDUSTRY.
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20. GENETIC RISKS AND ENVIRONMENTAL SURVEILLANCE: EPIDEMIOLOGICAL ASPECTS OF MONITORING INDUSTRIAL POPULATIONS FOR ENVIRONMENTAL MUTAGENS.
Buffler PA, Aase JM
Sch. Public Health, Univ. Texas Health Science Center at Houston, P.O. Box 20186, Houston, TX, 77025
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21. OSHA AT THE THRESHOLD: SETTING PERMISSIBLE EXPOSURE LEVELS FOR KNOWN CARCINOGENS AFTER AMERICAN PETROLEUM INSTITUTE.
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22. CARCINOGENESIS: PROBLEMS AND PARADOXES. THE 1981 GEORGE H. GEHRMANN LECTURE.
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CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

23. MODIFICATIONS OF CHROMATIN STRUCTURE IN CONTROL OF GENE EXPRESSION.
Hull LA
104 Depot St., New Sharon, IA, 50207
Med Hypotheses; 8(2):113-133 1982

24. PLASMINOGEN ACTIVATORS IN NEOPLASTIC CELLS.
Goloborod'ko OP, Veremeenko KN
A. I. Kolomiichenko Res. Inst. Otolaryngology, Kiev, USSR
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25. TUMOR PROMOTION BY REGENERATIVE EPIDERMAL HYPERPLASIA IN MOUSE SKIN.
Argyris TS
Dept. Pathology, Upstate Medical Center, State Univ. New York, Syracuse, NY, 13210
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26. SEX HORMONES AND LIVER CANCER.
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Institut National de Recherche, Centre de Recherche de Nancy, avenue de Bourgogne, F-54500 Vandoeuvre-les-Nancy, France
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TRANSFORMATION GENE STRUCTURE

1. NUCLEOTIDE SEQUENCE OF THE TRANSFORMING GENE OF SIMIAN SARCOMA VIRUS.

Devare SG, Reddy EP, Robbins KC, Andersen PR, Tronick SR, Aaronson SA
Lab. Cellular and Molecular Biology, Natl. Cancer Inst., Bethesda, MD, 20205
Proc Natl Acad Sci USA; 79(10,part1):3179-3182 1982

The sequence of the transforming region of simian sarcoma virus (SSV) has been determined by using molecularly cloned viral DNA. This region encompassed the 1.0-kilobase pair woolly monkey cell-derived insertion sequence, v-sis, and flanking simian sarcoma-associated viral (SSAV) sequences. A 675-nucleotide-long open reading frame commenced 19 nucleotides within the SSAV sequences to the left of the v-sis helper viral junction and terminated within v-sis itself. Possible promoter and acceptor splice signals were detected in helper viral sequences upstream from this open reading frame, and potential polyadenylylation sites were identified downstream both within v-sis and in helper viral sequences beyond v-sis. The recombinational event that led to the generation of SSV occurred in the middle of two functional codons, indicating that

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SSAV provided the regulatory elements for transcription as well as the initiation codon for translation of SSV cell-derived transforming sequences. (Author abstract) (28 Refs)

2. MOLECULAR CLONING OF THE FUJINAMI SARCOMA VIRUS GENOME AND ITS COMPARISON WITH SEQUENCES OF OTHER RELATED TRANSFORMING VIRUSES.

Shibuya M, Wang LH, Hanafusa H
Rockefeller Univ., New York, NY, 10021
J Virol; 42(3):1007-1016 1982

Full-length proviral DNA of Fujinami sarcoma virus (FSV) of chickens was molecularly cloned and characterized. An analysis of FSV DNA integrated in mammalian cells showed that restriction endonuclease SacI has a single cleavage site on FSV DNA. Unintegrated closed circular FSV DNA obtained from newly infected cells was linearized by digestion with SacI and cloned into lambdagtWES-lambdaB. The following three different molecules were isolated: FSV-1 (4.4 kilobases [kb]) and FSV-2 (4.7 kb), which appeared to be full-length FSV DNA molecules containing either one or two copies of the long terminal repeat structure, and FSV-3 (6 kb), which consisted of part FSV DNA and part DNA of unknown origin. An analysis of the structure of cloned FSV-1 and FSV-2 DNA molecules by restriction endonuclease mapping and hybridization with appropriate probes showed that about 2.6 kb of the FSV-unique sequence called FSV-fps is located in the middle of the FSV genome and is flanked by helper virus-derived sequences of about 1.3 kb at the 5' end and 0.5 kb at the 3' end. The long terminal repeats of FSV were found to have no cleavage site for either EcoRI or PvuI. Upon transfection, both FSV-1 DNA and FSV-2 DNA were able to transform mammalian fibroblasts. Four 32P-labeled DNA fragments derived from different portions of the FSV-fps sequence were used for hybridization to viral RNAs. We found that sequences within the 3' half of the FSV-fps gene are homologous to RNAs of PRCII avian sarcoma virus and the Snyder-Theilen strain of feline sarcoma virus, both of which were previously shown to contain transforming genes related to FSV-fps. These results suggest that the 3' portion of the FSV-fps sequence may be crucial for the transforming activity of fps-related oncogenic sequences. (Author abstract) (42 Refs)

3. ISOLATION AND CHARACTERIZATION OF C-MYC, A CELLULAR HOMOLOG OF THE ONCOGENE (V-MYC) OF AVIAN MYELOCYTOMATOSIS VIRUS STRAIN 29.

Vennstrom B, Sheiness D, Zabielski J, Bishop JM
Dept. Microbiology, Univ. Uppsala, Biomedical Center, Uppsala, Sweden
J Virol; 42(3):773-779 1982

The chicken genome contains nucleotide sequences homologous to the transforming genes (oncogenes) of a number of avian retroviruses. We have isolated chicken DNA (c-myc) that is homologous to the oncogene (v-myc) of the avian myelocytomatosis virus MC29 and have compared the structures of the cellular and viral genes. Results from restriction endonuclease mapping of c-myc and from analysis of heteroduplexes between the DNAs of the cellular and viral genes show that c-myc is homologous to 1,500 nucleotides in v-myc DNA. This homologous region is interrupted in c-myc by an intron-like sequence of 1,100 nucleotides which is absent from v-myc. Nuclear RNA from normal chicken cells contains at least five species of transcripts from c-myc ranging from 2.5 to 6.5 kilobases in length. By contrast, cytoplasm contains only the 2.5-kilobase c-myc RNA. These features of the c-myc gene and its nuclear transcripts are characteristic of normal cellular genes and suggest that the myc gene is of cellular rather than viral origin. The exons in c-myc may define two functional domains in the gene and may therefore facilitate the dissection of the different oncogenic potentials of the MC29 virus. (Author abstract) (28 Refs)

4. ISOLATION OF HUMAN ONCOGENE SEQUENCES (V-FES HOMOLOG) FROM A COSMID LIBRARY.

Groffen J, Heisterkamp N, Grosveld F, Van de Ven W, Stephenson JR

Lab. Viral Carcinogenesis, NCI, Frederick, MD, 21701

Science; 216(4550):1136-1138 1982

To define the human homolog (or homologs) of transforming sequences (v-fes gene) common to Gardner (GA) and Snyder Theilen (ST) isolates of feline sarcoma virus (FeSV), a representative library of human lung carcinoma DNA in a cosmid vector system was constructed. Three cosmid clones were isolated containing GA/ST FeSV v-fes homologous cellular sequences, within 32-to 42-kilobase cellular inserts representing 56 kilobases of contiguous human cellular DNA. Sequences both homologous to, and colinear with, GA or ST FeSV v-fes are distributed discontinuously over a region of up to 9.5 kilobases and contain a minimum of three regions of nonhomology representing probable introns. A thymidine kinase selection system was used to show that, upon transfection to RAT-2 cells, the human c-fes sequence lacked detectable transforming activity. (Author abstract) (24 Refs)

5. DEMONSTRATION OF BIOLOGICAL ACTIVITY AND NUCLEOTIDE SEQUENCE OF AN IN VITRO SYNTHESIZED CLONE OF THE MOLONEY MURINE SARCOMA VIRUS MOS GENE.

Donoghue DJ

Tumor Virology Lab., Salk Inst., San Diego, CA, 92138

J Virol; 42(2):538-546 1982

A clone of the Moloney murine sarcoma virus mos gene derived by in vitro reverse transcription was characterized. When assayed for focus formation by DNA transfection on NIH/3T3 cells, this clone was biologically inactive, presumably due to the absence of a long terminal repeat sequence. Therefore, a long terminal repeat was inserted into the clone by in vitro recombination, after which the mos gene was able to transform NIH/3T3 cells efficiently. The nucleotide sequence encompassing the transforming region of this clone was determined. A single long open reading frame was observed, which potentially encodes a polypeptide of 41,000 daltons. This open reading frame initiates with the first five amino acids of the murine leukemia virus env gene, after which it enters the mos sequence, where it terminates. The nucleotide sequences described in this paper was compared with other sequences of mos in an effort to resolve discrepancies in the position of the long open reading frame. Although Moloney murine sarcoma virus retains the 3' splicing site of the murine leukemia virus env gene, a mos-specific mRNA which corresponds structurally to the murine leukemia virus env mRNA was not identified. The sequence described here revealed a single nucleotide change in the proposed env gene 3' splicing site which was retained in Moloney murine sarcoma virus. This deviation from the consensus 3' splicing sequence may underlie the absence of mos expression via the env gene splicing pathway. (Author abstract) (44 Refs)

6. A GENERALIZED METHOD OF SUBCLONING DNA FRAGMENTS BY RESTRICTION SITE RECONSTRUCTION: APPLICATION TO SEQUENCING THE AMINO-TERMINAL CODING REGION OF THE TRANSFORMING GENE OF GAZDAR MURINE SARCOMA VIRUS.

Donoghue DJ, Hunter T
Tumor Virology Lab., Salk Inst., P.O. Box 85800, San Diego, CA, 92138
Nucleic Acids Res; 10(8):2549-2564 1982

The technique of restriction site reconstruction was generalized so as to allow the subcloning of any DNA fragment and its subsequent reexcision with EcoRI, XbaI, XhoI or HindIII. After excision, the 3' terminus of each strand will be derived from the starting nucleic acid, permitting the use of such fragments as primers for nucleotide sequencing by primer extension methods. The technique was used to subclone a 56 base pair BstNI-DdeI fragment of Moloney murine sarcoma virus (Mo-MSV) as a unique HindIII-HindIII fragment. This fragment then served as a primer to sequence a portion of the RNA genome of Gazdar murine sarcoma virus (Gz-MSV). The nucleotide sequence which was obtained indicated that the transforming gene of Gz-MSV arose by at least two recombination events involving murine leukemia virus (MLV) and the cellular homologue c-mos. This analysis suggests that a virus indistinguishable from Mo-MSV was an intermediate in the formation of Gz-MSV. (Author abstract) (31 Refs)

7. AVIAN SARCOMA VIRUS Y73 GENOME SEQUENCE AND STRUCTURAL SIMILARITY OF ITS TRANSFORMING GENE PRODUCT TO THAT OF ROUS SARCOMA VIRUS.

Kitamura N, Kitamura A, Toyoshima K, Hirayama Y, Yoshida M
(c/o Yoshida), Cancer Inst., Toshima-ku, Tokyo 170, Japan
Nature; 297(5863):205-208 1982

From the complete nucleotide sequence of the genome of the avian sarcoma virus Y73, we have predicted amino acid sequence of p90gag-yes, the product of the transforming gene. Contrary to previous evidence from molecular hybridization studies, p90gag-yes was found to have much homology with the transforming gene product p60src of Rous sarcoma virus, suggesting that the cellular counterparts of the two (c-yes and c-src) originated from a common prototype sequence. (Author abstract) (32 Refs)

8. CHANGE OF DNA NEAR THE ORIGIN OF REPLICATION ENHANCES THE TRANSFORMING CAPACITY OF HUMAN PAPOVAVIRUS BK.

Watanabe S, Yoshiike K
Dept. Enteroviruses, Natl. Inst. Health, Kamiosaki, Shinagawa-ku, Tokyo 141, Japan
J Virol; 42(3):978-985 1982

A turbid-plaque-forming mutant (pm522) of human papovavirus BK, which has a small deletion at about 0.7 map unit and grows somewhat more slowly in human cells than does wild-type BK virus, transformed hamster and rat cells in culture much more efficiently than did wild-type virus. Another plaque morphology mutant, pm525, forming turbid plaques larger than those of pm522 also had a high transforming capacity. The similar difference in transforming capability between wild-type and plaque morphology viruses was observed with DNAs extracted from virions. Recombinant viruses were constructed from the wild-type DNA fragment lacking HindIII-C (0.62 to 0.73 map unit) and pm522 HindIII-C (including the origin of replication) by the molecular cloning method. Characterization of the recombinants showed that the change near the origin of DNA replication was responsible both for the altered plaque morphology and for the enhanced transforming capacity of the BK virus mutant. (Author abstract) (33 Refs)

9. POLYOMA VIRAL MIDDLE T-ANTIGEN IS REQUIRED FOR TRANSFORMATION.

Mes AM, Hassel JA
(c/o Hassel) Dept. Microbiology and Immunology, McGill Univ., Montreal, Quebec H3A 2B4, Canada
J Virol; 42(2):621-629 1982

To determine whether small or middle T-antigen (or both) of polyoma virus is required for transformation, we constructed mutants of recombinant plasmids which bear the viral oncogene and measured the capacity of these mutants to transform rat cells in culture. Insertion and deletion mutations in sequences encoding small and middle T-antigens (79.7, 81.3, and 82.9 map units) rendered the DNA incapable of causing transformation by the focus assay. Similar mutations in sequences that encoded middle but not small T-antigen (89.7, 92.1, and 96.5 map units) generally abolished the transforming activity of the DNA. However, two mutants (pPdl1-4 and pPdl2-7) that carried deletions of 92.1 map units retained the capacity to transform cells; pPdl1-4 did so at frequencies equal to those of the parental plasmid, whereas pPdl2-7 transformed at 10% the frequency of its antecedent. From these studies we conclude that small T-antigen alone is insufficient to cause transformation and that middle T-antigen is required for transformation, either in combination with small T-antigen or by itself. (Author abstract) (43 Refs)

10. ONCOGENES IN HUMAN TUMOR CELL LINES: MOLECULAR CLONING OF A TRANSFORMING GENE FROM HUMAN BLADDER CARCINOMA CELLS.

Pulciani S, Santos E, Lauver AV, Long LK, Robbins KC, Barbacid M
Lab. Cellular and Molecular Biology, NCI, Bethesda, MD, 20205
Proc Natl Acad Sci USA; 79(9):2845-2849 1982

The presence of dominant transforming genes in human tumor cell lines has been investigated. High mol wt DNAs isolated from cell lines established from carcinomas and sarcomas of various organs as well as from a glioblastoma and two melanomas were utilized to transfect NIH/3T3 mouse fibroblasts. The DNAs of T24 and A2182, two cell lines derived from a bladder and a lung carcinoma, respectively, and of HT-1080, a cell line established from a fibrosarcoma, were able to transform recipient NIH/3T3 cells. First-cycle transformants exhibited anchorage-independent growth and were tumorigenic in athymic and immunocompetent mice. Moreover, they contained human DNA sequences and were able to transmit their malignant phenotype in additional cycles of transfection. Southern blot analysis of T24-derived transformants showed that a single fragment of human DNA specifically cosegregated with the malignant phenotype, suggesting that it contained the T24 oncogene. Therefore, these human sequences were molecularly cloned with lambda Charon 9A as the cloning vector. The resulting recombinant DNA molecule, designated lambdaT24-15A, was shown to contain a 15-kilobase-pair EcoRI insert of human cellular DNA. LambdaT24-15A DNA (either intact or EcoRI digested) transformed NIH/3T3 fibroblasts with a specific activity of 20,000 focus-forming units per pmol of cloned DNA. Our results indicate that we have molecularly cloned a biologically active oncogene present in T24 human bladder carcinoma cells. (Author abstract) (28 Refs)

11. GENE REGULATION AND ONCOGENESIS BY RETROVIRUSES (MEETING ABSTRACT)

Varmus HE
Department of Microbiology and Immunology, University of California, San Francisco, CA
Thirty-fifth Annual Symposium on Fundamental Cancer Research, March 2-5, 1982, Houston, Texas. The University of Texas M. D. Anderson Hospital and Tumor Institute 38 pp., 1982.

We studied the functional capacities of long terminal repeats (LTRs) by constructing recombinant plasmids, which contain LTRs and cloned genes in various arrangements, and then introducing them into cultured cells. As expected, only an LTR in the correct transcriptional orientation upstream from a promoter-less gene can produce expresson of that gene. However, when the gene carries its own promoter, the efficiency of DNA transformation is enhanced manyfold by the presence, in either orientation, of certain LTRs suggesting that some LTRs may enhance gene expression at distant, heterologous promoters in a nonpolar fashion. The LTR of mouse mammary tumor virus (MMTV) governs expression of viral or linked cellular genes in a glucocorticoid-responsive manner; the region responsible for hormonal regulation has been localized to about 0.4 kb near the 3' end of the MMTV LTR. The induction of B-cell lymphomas by avian leukosis virus (ALV) appears to require insertion of proviral DNA near c-myc, a putative cellular oncogene. The viral inserts, sometimes comprising little more than a single LTR, can enhance expression of c-myc in at least three arrangments: When positioned upstream from c-myc in the same transcriptional orientation, the inserts are promoters for the transcription of c-myc; when positioned upstream in the opposite orientation to c-myc or downstream in the same orientation, they enhance expression from unidentified cellular promoter(s). In the last instance, the LTR provides a novel site for polyadenylation. Interrupted c-myc loci have been cloned from tumor DNA and reintroduced into cultured cells to identify determinants of the enhancement phenomena. (no Refs)

12. ORIGIN, STRUCTURE, AND FUNCTION OF THE TRANSFORMING REGION ON THE ABELSON MURINE LEUKEMIA VIRUS (MEETING ABSTRACT)

Baltimore D, Wang J, Goff S, Queen C
Center for Cancer Research, Massachusetts Institute of Technology, Cambridge, MA
Thirty-fifth Annual Symposium on Fundamental Cancer Research, March 2-5, 1982, Houston, Texas. The University of Texas M. D. Anderson Hospital and Tumor Institute 38 pp., 1982.

The transforming region, V-abl, of the Abelson murine leukemia virus (A-MuLV) originates in a normal gene of the mouse, C-abl. C-abl represents a number of small regions of DNA that are homologous to V-abl separated by long stretches of DNA that are not. Our interpretation of this organization is that V-abl represents a cDNA copy of the exons that compose the C-abl gene and that the large nonhomologous regions represent introns that have been excised. V-abl joins the MuLV sequence in the A-MuLV genome at a precise point where there is a four-base homology between the Moloney murine leukemia virus (M-MuLV) sequence and the C-abl sequence. The joining position appears to be in the center of an exon of the C-abl gene. At the 3' end, the V-abl/M-MuLV joint is again precise, but the C-abl sequence has not been completed in that region. The organization of the transcripts of the C-abl gene indicates that the C-abl mRNA (of which there are two) has 400 bases 5' of the region homologous to V-abl and 2 to 3 kb 3' of the homologous region. All these structural facts can be reconciled by assuming that the A-MuLV genome arose through the integration of a M-MuLV genome upstream from the C-abl gene, followed by a deletion that brought the M-MuLV sequences in apposition to a C-abl exon. Transcription of this deleted gene from the M-MuLV promoter would then generate an RNA transcript with an M-MuLV 5' end. The final A-MuLV genome presumably arose by a secondary recombination at the reverse transcription level, according to the model of Goldfarb and Weinberg. In the context of the A-MuLV genome, the V-abl sequences encode a tyrosine-specific protein kinase activity. By expressing the V-abl region in Escherichia coli, the kinase activity has been shown to be intrinsic to the V-abl protein because in Escherichia coli the protein is phosphorylated on a tryosine residue. (1 Ref)

13. EXPRESSION OF TRANSDUCED GENES IN MAMMALIAN CELLS (MEETING ABSTRACT)

Berg P
Department of Biochemistry, Stanford University Medical Center, Stanford, CA
Thirty-fifth Annual Symposium on Fundamental Cancer Research, March 2-5, 1982, Houston, Texas. The University of Texas M. D. Anderson Hospital and Tumor Institute 38 pp., 1982.

Our laboratory has explored two approaches to achieving transduction-transformation of mammalian cells. One uses recombinants constructed in vitro from suitably modified cloned cDNAs or prokaryote and eukaryote-derived genomic segments and SV40 DNA from which segments encoding early and late viral functions have been excised. In this experimental design, the recombinant viral genomes must contain the origin of SV40 DNA replication and must not be larger than 5.3 kb in order to be propagated as mature virion genomes; moreover, since the recombinant genomes are defective, propagation can occur only with a helper virus to provide the missing gene product(s). A virtue of this approach is that amplification of the recombinant genomes ensures a high yield of the mRNAs and proteins expressed from the transduced genes. The second approach exploits a new group of transducing-transforming DNA vectors for the introduction and maintenance of new genes in a variety of mammalian cells. One prototype of this class of vectors, pSV2-neo, developed by Peter Southern and Bruce Howard, contains a DNA segment from the plasmid pBR322, in order to permit propagation of the recombinants in Escherichia coli, and a transcription unit comprising the SV40 early region promoter, the dominant selectable marker, Econeo, an intervening sequence, and a poly A site. Cells transformed with pSV2-neo (frequency, 10(-4) to 10(-5)) grow in media containing the inhibiting aminoglycoside G418. Unique restriction sites in pSV2-neo DNA permit the introduction of other, nonselectable genes into the same vector and, thereby, the cotransformation of cells for these otherwise nonselectable phenotypes. (no Refs)

TRANSFORMATION GENE EXPRESSION AND REGULATION

14. CARCINOGEN- AND RADIATION-TRANSFORMED C3H 10T1/2 CELLS CONTAIN RNAS HOMOLOGOUS TO THE LONG TERMINAL REPEAT SEQUENCE OF A MURINE LEUKEMIA VIRUS.

Kirschmeier P, Gattoni-Celli S, Dina D, Weinstein IB
Cancer Center/Inst. Cancer Res., Div. Environmental Science, Columbia Univ., New York, NY, 10032
Proc Natl Acad Sci USA; 79(9):2773-2777 1982

Carcinogen- or radiation-transformed C3H 10T1/2 murine fibroblasts transcribe a set of poly(A)+ RNAs that contain sequences homologous to the long terminal repeat (LTR) sequence of Moloney murine sarcoma virus. These LTR-containing RNAs consist of a series of discrete bands ranging in size from about 38 to 18 S. The higher mol wt molecules (30-38 S) in this set of RNAs also contain sequences homologous to the gag, pol, and env genes of a murine leukemia virus. A 24S RNA contains sequences homologous to the env gene of murine leukemia virus. A 20S and an 18S RNA also share homology with the LTR probe but fail to hybridize to the gag, pol, or env probes or to a probe for the U3 region of the LTR sequence. Thus, the latter transcripts do not appear to arise from a known endogenous murine leukemia virus genome. Although this entire set of RNAs is absent from normal C3H 10T1/2 cells (or is present at an extremely low level), these RNAs are induced by BrdUrd or 5-azacytidine. The presence of these RNAs may provide highly sensitive molecular markers of transformation of mouse cells. (Author abstract) (35 Refs)

15. DEPENDENCE OF TUMOR-FORMING CAPACITIES OF CELLS TRANSFORMED BY RECOMBINANTS BETWEEN ADENOVIRUS TYPES 5 AND 12 ON EXPRESSION OF EARLY REGION 1.

Shiroki K, Maruyama K, Saito I, Fukui Y, Yazaki K, Shimojo H
(c/o Shimojo) Inst. Medical Science, Univ. Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo, 108, Japan
J Virol; 42(2):708-718 1982

Recombinants between an adenovirus Type 5 (Ad5) deletion mutant and the Ad12 DNA fragment containing early Region 1 (E1) were isolated from cells cotransfected with the EcoRI-C fragments of Ad12DNA and Ad5 dl312 (deletion in E1A) DNA (rcA) and from cells cotransfected with the SalI-C fragment of Ad12 DNA and Ad5 dl312 DNA (rcB). No recombinant was isolated from cells cotransfected with Ad5 dl313 (deletion in E1B) DNA and restriction fragments of Ad12 DNA. Both rcA and rcB are defective and able to replicate in human embryo kidney (HEK) and KB cells with complementation by dl312. Both rcA and rcB formed Ad12 T antigen g, but not T antigen f, in infected HEK and KB cells. In rcA- and rcB-infected cells, Ad5 E1B and Ad12 E1A genes are transcribed. Heteroduplex and size analysis of rcA-1 or rcB-1 DNA fragments hybridized with Ad12 DNA revealed that rcA-1 DNA has a deletion between 5 and 15 map units with an insertion of a portion of Ad12 DNA (10%) and that rcB-1 DNA has a deletion between 70 and 80 map units with an insertion of a portion of Ad12 DNA (10%). The transformed cell lines, RCAY and RCBY, were established after infection of rat 3Y1 cells with rcA and rcB, respectively. Both Ad5 and Ad12 DNA sequences are contained in these cells. In RCAY cells, Ad12 T antigen g is detected, but Ad12 T antigen f is not. In RCBY cells, both Ad12 T antigens g and f are detected. Only the Ad12 E1A gene is transcribed in RCAY cells, whereas Ad5 E1B, Ad12 E1A, and Ad12 E1B genes are transcribed in RCBY cells. In soft-agar cultures, RCBY cells form large colonies, whereas RCAY cells form only tiny colonies. RCBY cells form tumors as efficiently as 12WY cells in transplanted rats. RCAY cells formed tumors inefficiently. Ad5-transformed 5WY cells do not form tumors. These observations indicate that the efficient tumor formation by RCBY cells is dependent on the expression of the Ad12 E1A and E1B genes, whereas the inefficient tumor formation by RCAY cells is due to the expression of only the Ad12 E1A gene. (Author abstract) (28 Refs)

16. IDENTIFICATION OF AN ANTIGEN ASSOCIATED WITH TRANSFORMING GENES OF HUMAN AND MOUSE MAMMARY CARCINOMAS.

Becker D, Lane MA, Cooper GM
(c/o Cooper), Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
Proc Natl Acad Sci USA; 79(10,part1):3315-3319 1982

Sera from tumor-bearing mice immunoprecipitated an 86,000-dalton glycoprotein from extracts of NIH cells transformed by human mammary carcinoma DNA. This antigen was not immunoprecipitated from extracts of NIH 3T3 cells, spontaneously transformed NIH cells, NIH cells transformed by normal human DNA, NIH cells transformed by human bladder carcinoma DNA, or NIH cells transformed by Rous sarcoma virus DNA. In addition, sera from mice bearing tumors induced by NIH cells transformed by either normal human DNA or human bladder carcinoma DNA did not immunoprecipitate this antigen from extracts of NIH cells transformed by human mammary carcinoma DNA. However, this antigen was immunoprecipitated by sera from mice bearing tumors induced by NIH cells transformed by mouse mammary carcinoma DNAs and from mice bearing primary mammary carcinomas. These results indicate that this glycoprotein represents an antigen that is specifically associated with expression of the transmissible transforming genes of human and mouse mammary carcinomas. (Author abstract) (15 Refs)

17. VIRAL SRC GENE PRODUCTS ARE RELATED TO THE CATALYTIC CHAIN OF MAMMALIAN CAMP-DEPENDENT PROTEIN KINASE.

Barker WC, Dayhoff MO
Natl. Biomedical Res. Foundation, Georgetown Univ. Medical Center, Washington, DC, 20007
Proc Natl Acad Sci USA; 79(9):2836-2839 1982

The transforming protein sequences translated from the Rous avian and Moloney murine sarcoma virus src genes are shown to be related to the catalytic chain of bovine cAMP-dependent protein kinase (ATP: protein phosphotransferase, EC 2.7.1.37). The avian transforming protein, also a protein kinase, shows greatest homology with the bovine protein kinase in the carboxyl-terminal half, where the protein kinase activity is localized. Moreover, lysine occurs in the inferred transforming protein sequences at the position homologous with the proposed ATP-binding lysine of the bovine protein kinase. This relationship is consistent with the hypothesis that the src genes originated in the host genomes, in which they are members of a superfamily of distantly related protein kinases that are normal constituents of mammalian cells. In the host, these sequences are much more highly conserved than in the viruses. (Author abstract) (16 Refs)

18. CHARACTERIZATION OF THE AVIAN SARCOMA VIRUS TRANSFORMING GENE PRODUCTS (MEETING ABSTRACT)

Erikson RL, Gilmer TM, Erikson E, Arrigo AP, Foulkes JG, Granot Y
Department of Pathology, University of Colorado School of Medicine, Denver, CO, 80262
Conference on Cell Proliferation, Cancer and Cancer Therapy, February 17-19, 1982, New York, New York New York Academy of Sciences; :A24 1982

The Rous sarcoma virus transforming gene product (pp60src) and its normal cell homologue both appear to be protein kinases with the capacity to phosphorylate tryosine residues in various protein substrates. Investigations in several laboratories have shown that at least three other classes of avian sarcoma viruses exist each with a unique transforming gene encoding transforming gene products with associated tyrosine-specific phosphotransferase activity. Some of these transforming gene products have been purified extensively and the nature of their associated enzymatic activities will be discussed. Studies on radiolabeled phosphoproteins in infected cells show that dephosphorylation of phosphotyrosine can occur very rapidly, thus suggesting the existence of a phosphotyrosine phosphatase(s). Progress in the purification of the relevant enzymes and their activities, particularly toward pp60src, will be discussed. (no Refs)

19. TWO RETROVIRUSES WITH SIMILAR TRANSFORMING GENES EXHIBIT DIFFERENCES IN TRANSFORMING POTENTIAL.

Linial M
Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
Virology; 119(2):382-391 1982

The genomes of MH2 and MC29 have been shown to be highly similar and contain the same oncogenic sequence termed myc. Both viruses can transform Japanese quail (Coturnix coturnix japonica) embryo fibroblasts and mature peripheral blood macrophages in vitro. However, a striking difference is observed after in vivo infection of 3-wk-old quail. Neither virus causes either sarcomas or myelocytomas. MC29 is only weakly oncogenic; only 2 of 29 birds developed tumors which were localized in the liver. In contrast MH2 is highly oncogenic; birds generally developed solid tumors near the site of injection, or liver tumors. When the solid tumors were placed in culture they gave rise to transformed macrophages, and surprisingly, erythrocyte-like cells, which were not transformed. MH2 and MC29 also exhibited different efficiencies of macrophage and fibroblast transformation in vitro. It is postulated that the biological differences between the two viruses could be related to differences in processing of myc sequences. (Author abstract) (22 Refs)

20. IDENTIFICATION AND CHARACTERIZATION OF A TUMOR-SPECIFIC ANTIGEN EXPRESSED BY RETICULOENDOTHELIOSIS VIRUS-TRANSFORMED HEMATOPOIETIC CELLS (MEETING ABSTRACT)

Walker MH, Neisel DW, Bose HR
Microbiology Department, University of Texas, Austin, TX, 78712
Fed Proc; 41(3):897 1982

Birds infected with avian reticuloendotheliosis virus (REV-T) develop a fatal, acute lymphocytic leukemia within 7 to 14 days. The target cell for this replication-defective acute leukemia virus has been characterized as an immature lymphocyte expressing some B-cell determinants. Using 125I/hydrogen peroxide/lactoperoxidase cell-surface labelling and radioimmunoprecipitation with antiviral antisera, we have identified a polypeptide of 120,000 daltons (p120) that is expressed by each of 17 independently-derived clones of REV-T transformed lymphocytes. Furthermore, all clones of REV-T transformed nonvirus-producing lymphocytes which have been isolated do not synthesize detectable levels of viral structural polypeptides but do express p120. Therefore, we have characterized the structural relationship between p120 expressed by nonvirus-producing REV-T transformed clones and the viral envelope, major core and gag-pol precursor polypeptides by thin-layer peptide mapping. (no Refs)

21. MUTANT OF SIMIAN VIRUS 40 LARGE T-ANTIGEN THAT IS DEFECTIVE FOR VIRAL DNA SYNTHESIS, BUT COMPETENT FOR TRANSFORMATION OF CULTURED RAT CELLS.

Stringer JR
Cold Spring Harbor Lab., Cold Spring Harbor, NY, 11724
J Virol; 42(3):854-864 1982

A mutant was isolated which demonstrates that the transforming activity of simian virus 40 large T-antigen is separable from its function in viral DNA replication. The mutant, SVR9D, is nonconditionally defective for viral DNA synthesis, but competent at wild-type level for morphological transformation of cultured rat cells. The lytic growth defect in SVR9D is complemented by the simian virus 40 A gene product present in the transformed CV1 cell line, COS1. The lesion in SVR9D DNA was mapped genetically by marker rescue of plaque formation and localized to a 214-base-pair segment of the viral genome bounded by nucleotide numbers 4100 and 4314. DNA sequence analysis showed the mutation to be an adenine-to-guanine transition at nucleotide number 4178. This change predicts a lysine-to-glutamic acid amino acid change at residue number 214 of the mutant large T-antigen polypeptide. (Author abstract) (32 Refs)

22. PRODUCTION OF A T-ANTIGEN-RELATED PROTEIN IN MAMMALIAN CELLS AFTER STABLE TRANSFORMATION WITH A CLONED SV40 GENE FRAGMENT.

Horst J, Jacob E, Weckler C, Deppert W
Abteilung Humangenetik, Universitat Ulm, Oberer Eselsberg, D-7900 Ulm, W. Germany
Hoppe Seylers Z Physiol Chem; 363(4):445-448 1982

A recombinant plasmid based on pBR322 has been constructed which carries the replicator proximal early region of SV40 DNA, including the viral origin of replication (ORI). It lacks a major part of the tumor antigen 3'-coding region, the large T-antigen termination codon and the polyadenylation site. The recombinant plasmid was transferred together with the herpes simplex virus thymidine kinase gene, as a selectable marker into mouse LTK- cells. Integration and expression of the cloned SV40 gene fragment in TK+ transformants could be demonstrated by DNA restriction and blot hybridization and by immunofluorescence techniques. (Author abstract) (12 Refs)

23. EXPRESSION OF THE GENE ENCODING THE ADENOVIRUS DNA TERMINAL PROTEIN PRECURSOR IN PRODUCTIVELY INFECTED AND TRANSFORMED CELLS.

Binger MH, Flint SJ, Rekosh DM
Dept. Biochemical Sciences, Princeton Univ., Princeton, NJ, 08544
J Virol; 42(2):488-501 1982

The major product of in vitro translation of early RNA prepared from H5ts125-infected cells and selected by hybridization to adenoviral DNA fragments spanning the region from 14.7 to 31.5 map units has been shown to be identical to the 87-kilodalton terminal protein precursor. A 72-to 75-kilodalton polypeptide whose mRNA can be selected by DNA from this region and made in the presence of anisomycin was indistinguishable from the 72-kilodalton single-stranded DNA-binding protein encoded by the region from 60.1 to 66.6 map units. The accumulation of cytoplasmic RNA sequences complementary to these l-strand genes under various conditions of infection and in certain lines of transformed cells has been investigated by solution hybridization of cytoplasmic RNA to the separated strands of restriction endonuclease fragments of adenoviral DNA. During the early phase, RNA sequences complementary to the region from 11.6 to 36.7 map units were present at a concentration of 10 to 60 copies per cell, regardless of the nature of the block used to inhibit viral DNA synthesis. By 24 hr after infection in the absence of any such block, sequences complementary to the regions from 11.6 to 18.2 map units (IVa2) and from 18.6 to 36.7 map units (E2B) accumulated to concentrations of 4,800 and 280 copies per cell, respectively. The ratio of cytoplasmic E2A RNA sequences to E2B RNA sequences remained close to 10:1 throughout the time period investigated. Of the transformed cell lines which retained E2B DNA sequences that were examined, only the T2C4 line expressed these sequences in cytoplasmic RNA. The implications of these observations for regulation of expression of the adenoviral early l-strand genes are discussed. (Author abstract) (73 Refs)

24. IDENTIFICATION OF PROTEINS ENCODED BY A FRAGMENT OF HERPES SIMPLEX VIRUS TYPE 2 DNA THAT HAS TRANSFORMING ACTIVITY.

Galloway DA, Goldstein LC, Lewis JB
Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
J Virol; 42(2):530-537 1982

Cloned BglII fragment N (map units 0.58 to 0.625) of herpes simplex virus Type 2 DNA has been shown to transform rodent cells to an oncogenic phenotype. RNA homologous to this fragment directs the synthesis of five polypeptides in a cell-free translation system. The approx mol wt of these proteins are 140,000, 61,000, 56,000, 35,000, and 23,500. The 35,000-dalton protein is the major species late in infection and is the only species detected before the onset of viral DNA replication. The arrangement of the sequences encoding these proteins along the herpes simplex virus Type 2 genome was determined by hybridization of the RNA to cloned PstI fragments of BglII-N and to single-stranded DNA segments cloned into M13mp7. Both the hybridization experiments and immunoprecipitation with monoclonal antibodies suggested that the 140,000-and 35,000-dalton proteins are at least partially colinear and share antigenic determinants. (Author abstract) (41 Refs)

25. GENETIC ANALYSIS OF TUMORIGENESIS. VIII. SUPPRESSION OF SV40 TRANSFORMATION IN CELL HYBRIDS AND CYTOPLASMIC TRANSFERANTS.

Howell N, Sager R
Joint Center for Radiation Therapy, Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
Cytogenet Cell Genet; 31(4):214-227 1981

Intraspecies somatic cell hybrids of BALB/c mouse 3T3 and SV40-transformed embryonic fibroblast (SVT2) cells were analyzed for transformation-associated properties and their tumorigenic potential in nude mice. In confirmation of our earlier findings, hybrids expressing the viral T-antigen were not suppressed for the ability to clone in medium with 1% serum. In contrast, division rate in medium with 1% and 10% serum, anchorage independence, cytochalasin-sensitive growth control, and tumorigenicity were suppressed noncoordinately, and the extent of suppression varied from one hybrid to another. Suppression was not simply determined by the increased chromosome content of the hybrid cells, nor was suppression correlated with rearrangements of the integrated viral sequence. Similar results were found in cytoplasmic transferants expressing T-antigen. Four independent transferants and subclones derived from them varied in the extent of suppression of anchorage independence and tumorigenicity. In both hybrids and transferents, a low serum requirement for clonal growth apparently was determined solely by expression of SV40 T-antigen, but other transformation properties, as well as tumorigenicity, appeared to require multiple changes in the cellular genome for their expression. These changes must occur during or after viral integration, since they are not expressed in uninfected 3T3 cells. (Author abstract) (47 Refs)

GENETIC AND OTHER HOST FACTORS WHICH MODULATE ONCOGENIC TRANSFORMATION

26. GENETIC ANALYSIS OF FAMILIAL CANCERS (MEETING ABSTRACT)

White R, Barker D, Cavenee W, Skolnick M
Department of Cellular, Viral, and Molecular Biology, University of Utah School of Medicine, Salt Lake City, UT
Thirty-fifth Annual Symposium on Fundamental Cancer Research, March 2-5, 1982, Houston, Texas. The University of Texas M. D. Anderson Hospital and Tumor Institute 38 pp., 1982.

Families that have a marked predisposition to the development of specific tumors, such as retinoblastoma, Wilms' tumor, and colon and breast cancer, may carry and segregate specific alleles at loci that interact with the biochemical pathway and thus lead to tumorigenesis. Genetic analysis of these individuals at both the organismal and cellular levels will provide the basis for a molecular genetic approach to the etiology of such tumors. The necessity of knowing the genotype of both individuals and their tumors can be met by genetic markers based on DNA sequence polymorphism. Markers defining arbitrary loci can be used in familial studies to confirm the genetic basis of observed familial clustering and to examine genetic events in tumors. DNA segments containing suspected oncogenes (for example, the human equivalents of the genes defined in animal cells transformed by retroviruses or in cells transformed with DNA isolated from tumors) can be used to develop polymorphic restrction fragment markers and, in turn, to determine the role of such oncogenes in the primary etiology of familial tumors. We will report our progress in using these approaches to study retinoblastoma and colon cancers. (no Refs)

27. ECOTROPIC MURINE LEUKEMIA VIRUS DNA CONTENT OF NORMAL AND LYMPHOMATOUS TISSUES OF BXH-2 RECOMBINANT INBRED MICE.

Jenkins NA, Copeland NE, Taylor BA, Bedigian HG, Lee BK
Jackson Lab., Bar Harbor, ME, 04609
J Virol; 42(2):379-388 1982

BXH-2 recombinant inbred mice spontaneously produce a B-tropic murine leukemia virus (MuLV) beginning early in life and have a high incidence of non-T-cell lymphomas. These traits are not characteristic of the progenitor strains (C57BL/6J and C3H/HeJ) or of 11 other BXH recombinant inbred strains. Since B-tropic virus expression may be causally related to the high incidence of lymphoma in this strain, we have analyzed the ecotropic MuLV DNA content of both normal and lymphomatous tissues of BXH-2 mice. Southern analysis and hybridization with an ecotropic MuLV DNA-specific probe showed that DNA of normal BXH-2 tissues contained both parental N-tropic MuLV proviruses but lacked endogenous B-tropic MuLV DNA sequences. In addition, none of 116 F1 hybrid mice derived from male BXH-2 mice spontaneously produced ecotropic MuLV early in life. These results suggest that the B-tropic virus is horizontally transmitted in BXH-2 mice. Southern analysis of DNA from tumor tissues of 12 BXH-2 mice showed that amplification of ecotropic-specific DNA sequences had occurred in lymphomatous tissues of 3 mice and suggested that these tumors were monoclonal. The number of newly acquired proviruses, which appeared to be structurally nondefective and integrated at different sites, varied from one to three copies. Since lymphomatous tissues, from only 3 of 12 mice examined carried additional detectable ecotropic proviruses, these results suggest that amplification of ecotropic MuLV DNA sequences if not required for maintenance of transformation in BXH-2 lymphomas. (Author abstract) (36 Refs)

28. SEPARATION OF HIGH MAMMARY TUMOR INCIDENCE FROM HIGH HEPATOMA INCIDENCE IN BACKCROSS MICE DURING SEGREGATION OF THE VIABLE YELLOW GENE.

Smith GH, Vlahakis G
Lab. Molecular Biology, NCI, Bethesda, MD, 20205
Int J Cancer; 29(5):587-590 1982

Mammary tumorigenesis in strain C3H/AvyfB female mice (approx 90% incidence) is not due to exogenous mouse mammary tumor virus (MMTV) but to genetic factors transmitted by either parent. Prominent among these genetic factors is the viable yellow (Avy) gene which may increase either the virulence of the endogenous MMTV provirus (Mtv-1) by promoting expression of the susceptibility of the mammary tissue to tumorigenesis by endogenous MMTV. Unexpectedly, the F1 hybrid females (AvyA) developed mammary tumors at a relatively low rate although hepatoma incidence remained high. Both yellow (AvyA) and agouti (AA) backcross females showed an even greater reduction in mammary tumor incidence, 7.9% and 3.8% respectively. In contrast, the high rate of spontaneous hepatoma development segregated with the Avy gene since 86-5% of the yellow (AvyA) backcross females development hepatomas by 19 mo of age, while only 25% of the agouti (AA) backcross females had liver tumors at 24.4 mo. The reduction of mammary tumor incidence in (C3H-AvyfB x C3H/Sm)F1 hybrids was unexpected since earlier studies had shown that reciprocal F1 hybrids between strains BALB/c and C3H-AvyfB continued to show a 90% mammary tumor incidence. The present result is consistent with the possibility that strain C3H/Sm possesses a heritable factor(s) which attenuates the ability of endogenous MMTV to malignantly transform mammary epithelium. (15 Refs)

29. SUSCEPTIBILITY OF BALB/CGNDU MICE TO TRANSPLANTABLE TUMORS, IN VITRO TRANSFORMED CELLS, BK AND SV40 VIRUSES, AND CHEMICAL CARCINOGENS.

Morrison DG, Moyer MP, Lynd FT, Rogers W, Moyer RC
Thorman Cancer Res. Lab., Trinity Univ., 715 Stadium Drive, San Antonio, TX, 78284
Oncology; 39(4):228-233 1982

Various oncogenic agents were employed in tumor susceptibility studies of an inbred subline of BALB/cGn mice, BALB/cGnDu, which carries a mutant gene that results in spontaneous thymic involution in homozygous recessive individuals. Of 18 transplantable tumors, 3 in vitro transformed cell lines, 2 oncogenic papovaviruses and 3 chemical carcinogens evaluated, only the Harding-Passey amelanotic melanoma produced tumors in 100% of the normal adult mice injected. The S180 pleomorphic sarcoma produced tumors in 56% of normal adult mice. Although not tumorigenic in adults, the mKSA, Morris (rat) hepatoma Number 7777, and a human papovavirus-transformed human cell induced mouse tumor line [GI110(BK) B6D2 Tu] formed tumors in 100, 62 and 70%, respectively, of recipients inoculated as neonates. SV40 and human papovavirus BK virions, as well as SV40, BK, and spontaneous in vitro transformed BALB/cGnDu cells were not tumorigenic. Although the histocompatibility antigens of these animals have not been studied, no correlations could be made between the tumor susceptibility of these animals with regard to the commonly employed inbred line BALB/c nor with regard to the range of host susceptibility of the transplantable tumors. This inbred subline represents a new strain of mice whose genetic defect makes it useful for transplantation immunology and physiological genetics. (Author abstract) (13 Refs)

30. GENETICS: ANIMAL TUMORS.

Heston WE
Lab. Biology, NCI, NIH, Bethesda, MD
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Genetics has helped determine that cancer is not a single disease but a group of different diseases. Genetics has helped integrate the approaches to cancer research for each approach has had to take into account genetic elements. Same form of tumor occurs in the most lowly multicellular organism with little normal cell differentiation, which indicates that the basic neoplastic change involves a very primitive physiological process. Tumors have been studied extensively in invertebrates such as the diploblastic coelenterates and insects. There is evidence among the vertebrates that in the evolution of the species certain gene complexes have been sorted out to give rise to specific tumors in certain species. Tumors have been studied in fish, fowl, birds, and mammals, particularly the rat and mouse. Selectivity of the species has been demonstrated through hybridization studies which indicate that cancer is a negative selective factor in the evolution of species. Inbreeding has been used in cancer research to provide high tumor strains of animals. Other topics reviewed are the genetics of spontaneous tumors, of chemically induced tumors, of hormonally induced tumors, and of virally-induced tumors. (90 Refs)

EXPERIMENTAL MODULATION OF ONCOGENIC TRANSFORMATION

31. TRANSFORMATION INDUCED BY ABELSON MURINE LEUKEMIA VIRUS INVOLVES PRODUCTION OF A POLYPEPTIDE GROWTH FACTOR.

Twardzik DR, Todaro GJ, Marquardt H, Reynolds FH, Stephenson JR
Lab. Viral Carcinogenesis, NCI, Frederick, MD, 21701
Science; 216(4548):894-897 1982

Rat embryo fibroblasts transformed by Abelson murine leukemia virus (MuLV) produce and release a transforming growth factor (TGF). Production of this factor is correlated with a tyrosine-specific protein kinase that is functionally active and is associated with the major Abelson MuLV gene product, P120. Transformation-defective mutants of Abelson MuLV do not transform cells, do not have their virus coded transforming gene product phosphorylated in tyrosine, and do not induce TGF production. Abelson MuLV-induced TGF morphologically transforms cells in culture, competes with 125I-labeled epidermal growth factor (EGF) for binding to cell receptors, and induces phosphorylation of tyrosine acceptor sites in the 160,000-dalton EGF membrane receptor. After purification to homogeneity, Abelson virus-induced TGF migrates as a single polypeptide with an apparent size of 7,400 daltons as determined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. (Author abstract) (27 Refs)

32. REGULATION OF INTRACELLULAR PROTEIN DEGRADATION BY INSULIN AND GROWTH FACTOR.

Ballard FJ, Nield MK, Francis GL, Knowles SE
CSIRO Div. Human Nutrition, Kintore Ave., Adelaide S. A. 5000, Australia
Acta Biol Med Ger; 40(10/11):1293-1300 1981

Some of the properties of growth factor (GF) action on protein breakdown (PBD) in cultured cells are described. Insulin, epidermal GF (EGF), fibroblast GF (FGF), insulin-like GF 1 (IGF-1), insulin-like GF 2 (IGF-2), and fetal calf serum (FCS) were tested for inhibitory effects on PBD in 19 cell lines. Examples of cells which are sensitive to other GF are presented. PBD in all cells tested was inhibited by FCS, IGF-1, and IGF-2. GF produce a stimulation of DNA synthesis. The addition of IGF-1 to HTC hepatoma cells showed that withdrawal of GF is accompanied by a rapid change to the higher rate of PBD. Marked inhibitions of PBD were observed in HTC hepatoma cells with insulin, IGF-1, and FCS but when these GF are added to the cells at concentrations known to give maximal effects, no additivity was observed. Concentration effects of GF in IMR90 fibroblasts, HTC, and MH1C1 hepatoma cells are presented. When effects of both insulin and IGF are considered together, PBD is reduced selectively in transformed cells. PBD is much more effectively inhibited by insulin, EGF, IGF-1, IGF-2, or FCS in the mid-passage than in the senescent cells. The poorer response does not appear to reflect an already low rate of autophagic proteolysis in the aged cells because inhibition of lysosomal proteolysis by ammonia gives an equal response in both mid-passage and aged cells. PBD is inhibited by 0.5% colostrum to approx the same extent as found with 10% FCS in six lines and only slighty less in MCF7 and OS104 cells. In both the H35 hepatoma and Swiss 3T3 mouse fibroblasts, 0.5% colostrum is more effective than 10% FCS. (9 Refs)

33. TUMOR CELL GROWTH FACTOR(S) ASSOCIATED WITH AN ESTROGEN-RESPONSIVE RAT MAMMARY TUMOR GROWING IN VIVO (MEETING ABSTRACT)

Leland F, Sirbasku DA
Department of Biochemistry, University of Texas Medical School, Houston, TX, 77025
Proc Am Assoc Cancer Res; 23:936 1982

Growth factors have been identified in extracts of MTW9/PL rat mammary tumor cells growing in vivo in response to estrogens. MTW9/PL tumors from intact females and from both estrogen treated castrated females and males had equivalent growth activity. Tumor extract protein added to serum-free DME at 10 ug/ml promoted significant MTW9/PL growth; 100 to 200 ug/ml replaced 75 to 100% of MTW9/PL serum requirement. Molecular properties of the tumor associated growth activity appear to be distinct from mammary growth factor activities in rat uterine, kidney, and pituitary tissues. The tumor activities show apparent molecular weights of 80,000 and 50,000 daltons on G-100 Sephadex and by heat, protease, and pH treatment, appear to be proteins. These activities are not due to residual serum and are not replaceable by known growth factors or hormones. Estrogens appear to influence directly growth factor activity level in MTW9/PL tumors since ovariectomy led to tumor regression and activity lower than that of tumors which are hormone autonomous or are growing in intact females. Our data suggest: 1) MTW9/PL tumor growth factors are related to estrogen levels in vivo; 2) autonomous tumors may produce growth factors continuously; 3) transformation from normal mammary gland to the neoplastic state includes the appearance of tumor associated growth factor. (no Refs)

34. COMPARATIVE EFFECTIVENESS OF THE ANTICARCINOGENIC AND TUMOR GROWTH INHIBITORY ACTIVITIES OF LYMPHOTOXIN, AN IMMUNOLOGIC HORMONE AND LYMPHOKINE (MEETING ABSTRACT)

Evans CH, Heinbaugh JA, DiPaolo JA
National Institutes of Health, Bethesda, MD, 20205
Fed Proc; 41(3):494 1982

The ability of lymphotoxin to prevent morphologic transformation induced by uv-irradiation or chemical carcinogen was contrasted with lymphotoxin inhibition of transformed cell growth to further assess the antineoplastic properties of this lymphokine. Syrian hamster peritoneal leukocytes were stimulated with phytohemagglutinin for 24 hr, the lymphokines diafiltered, and lymphotoxin purified by isoelectric focusing and HPLC (high performance liquid chromatography). Lymphotoxin cytolytic units were determined by measuring 3H-TdR (thymidine) release from mouse L cells. Hamster embryo cells (HEC) seeded for colony formation in culture dishes were treated simultaneously with carcinogen and lymphotoxin, and morphologic transformation quantitated after 7 days growth. Tumor producing cell lines derived from transformed colonies were cultured in reconstruction experiments with HEC and lymphotoxin, and the frequency of transformed colonies determined at 7 days. Lymphotoxin irreversibly inhibited carcinogen induced transformation with 6 units/ml reducing the transformation frequency 50%. Lymphotoxin inhibition of tumor cell growth, however, was reversible when growth following a 24 hr pulse of lymphotoxin was compared with 7 day exposure. A 50% reduction in tumor cell growth in 3 transformed lines, moreover, required 124, 330, and 477 units/ml, demonstrating that the anticarcinogenic activity of lymphotoxin can be 20+ fold greater than its tumor growth inhibitory activity. (no Refs)

35. PREVENTION OF TRANSPLACENTAL CARCINOGENESIS BY THE IMMUNOLOGIC HORMONE LYMPHOTOXIN (MEETING ABSTRACT)

Ransom JH, Evans CH, DiPaolo JA
National Institute of Health, Bethesda, MD, 20205
Fed Proc; 41(3):379 1982

Development of interventive measures to control cancer would be facilitated by monitoring carcinogenesis in vivo with an in vitro assay of morphologic transformation. Syrian hamsters at the 10-11th day of gestation were injected ip with 3 mg diethylnitrosamine (DEN)/100 g. Two days later, fetuses were excised, the fetal cells dissociated and 2000 cells seeded/60 mm dish for colony formation. The frequency of morphologically transformed colonies was determined after 7 days. The mean transformation frequency per cell seeded was 1 x 10(-4) with a 3.6% efficiency of colony formation. Ip injection of an immunologic hormone preparation reduced the trassformation frequency by 46%. The preparation was the diafiltered and concentrated lymphokines of phytohemagglutinin stimulated hamster peritoneal leukocytes. It contained 10,000 units of lymphotoxin but no detectable interferon. When DEN exposed cells were x-irradiated with 250 R in vitro and 9000 cells seeded/dish, an increased mean transformation frequency, corrected for x-ray toxicity, of 8.5 x 10(-4) per cell seeded was observed. The DEN + x-ray cocarcinogenic frequency of transformation was reduced 64% by ip injection of the immunologic hormone. This study indicates that immunologic hormones (eg lymphotoxin) can prevent carcinogenesis in vivo and that the in vitro quantitation of transformation provides a means for assessing passively administered and autochthonous effector mechanisms which control carcinogenesis in vivo. (no Refs)

36. CHEMICAL INTERACTIONS WITH HERPES SIMPLEX TYPE 2 VIRUS: ENHANCEMENT OF TRANSFORMATION BY NORHARMAN.

Johnson FB
Dept. Microbiology, Brigham Young Univ., Provo, UT, 84602
Carcinogenesis; 3(4):457-459 1982

The effects of the comutagen norharman on herpes simplex virus Type 2 growth transformation was studied in 3T3 cells. Pre-exposure but not post-exposure of the cells to 0.5 to 10 ug of norharman per ml of cell culture media resulted in a nearly three-fold enhancement in transforming activity. These results suggest that certain environmental chemicals may interact with cells creating an increased possibility of transformation by herpes viruses. (Author abstract) (27 Refs)

37. CHEMICAL INTERACTIONS WITH HERPES SIMPLEX TYPE 2 VIRUS: ENHANCEMENT OF TRANSFORMATION BY HYDRAZINE AND 1,2-DIMETHYLHYDRAZINE.

Johnson FB
Dept. Microbiology, Brigham Young Univ., Provo, UT, 84602
Chem Biol Interact; 40(1):97-112 1982

Quantitative assays for the morphological transformation of 3T3 Swiss mouse cells by herpes simplex Type 2 virus (HSV-2) were employed to examine the effect on cell transformation of chemical carcinogens and suspected carcinogens. Exposure of the cells to the chemical compound, followed by virus infection, resulted in enhancement of transformation when compared to that observed with chemical or virus alone. Enhancement occurred in tests utilizing either UV light-inactivated HSV-2 (strain 333) or a temperature-sensitive (ts) mutant of HSV-2 [A8(293)]. A series of seven ts-mutants were tested and exhibited varying degrees of transformation. Enhancement of transformation occurred in cells treated with hydrazine (HZ) and 1,2-dimethylhydrazine (SDMH). No enhancement occurred when cells were treated with monomethylhydrazine, 1,1-dimethylhydrazine and the jet fuels JP-5, JP-10, RJ-4 and RJ-5. A strong time dependence after treatment was demonstrated with some enhancement seen at 6 hr after chemical treatment but the greatest enhancement appeared when virus infection began after 24 hr of chemical exposure. (Author abstract) (25 Refs)

38. EFFECT OF CHEMICAL MUTAGENS ON HERPES VIRUS-INDUCED CELLULAR TRANSFORMATION AND TESTING FOR MUTAGENESIS IN MOUSE CELLS.

Johnson FB
Dept. Microbiology, Brigham Young Univ., Provo, UT
Effect of Chemical Mutagens on Herpes Virus-induced Cellular Transformation and Testing for Mutagenesis in Mouse Cells. Available from National Technical Information Service, Springfield, VA, as AD-A102 854/7:, 17 pp., 1981.

The temperature sensitive (ts) mutant A8(293) of herpes simplex Type 2 virus (HSV-2) was employed in tests to detect chemical interactions with the virus causing increased transformation of target cells. Mouse 3T3 cells were monitored for morphological transformation. Hydrazine and 1,2-dimethylhydrazine caused an enhancement of viral transformation of between three to four fold, confirming earlier findings using ultraviolet light inactivated wild type virus. Norharman (pH-pyrido(3,4-6)indole), a component to tobacco tars, caused a nearly three-fold enhancement of transformation. Xylene and tolulene were not found to enhance viral transformation. Experiments involving host-mediated activation of the test chemicals were unsuccessful because of low target cell recovery due to inhibition of the target 3T3 cells. (Author abstract)

39. STUDIES ON THE MECHANISM OF THE ANTIPROLIFERATIVE EFFECT ON INTERFERON (MEETING ABSTRACT)

Bilello JA, Pitha PM
The Johns Hopkins Oncology Center, Baltimore, MD
Conference on Cell Proliferation, Cancer and Cancer Therapy, February 17-19, 1982, New York, New York New York Academy of Sciences; :AP-2 1982

A number of in vivo and in vitro studies have indicated that cellular proliferation is inhibited in the presence of interferon. We have undertaken studies to determine what constitutes the effect of interferon on cell growth. To this end, we have characterized the synthesis, processing, phosphorylation and glycosylation of cellular and viral proteins in murine erythroleukemia cells. Treatment of Friend erythroleukemia cells with 250-5000 units of highly purified fibroblast interferon leads to a dose dependent inhibition of cell multiplication which is maximal between 24 and 48 hrs. The synthesis of the Friend virus transformation protein was normal at all doses of interferon tested. Pulse-chase analysis of 35S-methionine labeled Friend virus envelope glycoprotein precursor indicated that synthesis and processing were indistinguishable in the presence and absence of interferon. Analysis of glycopeptide patterns from control and interferon treated cells indicated no inhibition of N-linked glycosylation upon interferon treatment. Use of interferon sensitive and resistant cell lines have revealed interferon induced changes in plasma membrane structure and function. (no Refs)

40. INTERFERON-INDUCED CHANGES IN THE EXPRESSION AND TOPOGRAPHY OF H-2 ANTIGENS AND RECEPTORS FOR SRBC IN TUMOUR CELLS.

Capkova J, Peknicova J, Hajnicka V, Borecky L
Inst. Molecular Genetics, Czechoslovak Acad. Sciences, 142 20 Praha, Czechoslovakia
Folia Biol (Praha); 28(1):28-42 1982

The expression of the H-2 antigens and its changes after interferon (IFN) treatment were studied in methylcholanthrene (MCA) and mouse sarcoma virus(MSV)-transformed clones of C3H mouse embryonic fibroblasts. Topography of H-2 antigenic determinants on the cell membrane and the availability of receptors for sheep red blood cells (SRBCs) were also studied. Both MCA- and MSV-treated cells absorbed anti-H-2.23 (H-2Kk) antibody more effectively than did the control C3H cells; the MCA-treated cells were more effective than the MSV-treated clone. After IFN treatment, one MCV-treated clone showed increased absorbing capacity for H-2DK antibody, and that clone plus another showed increased absorbing capacity for H-2Kk antibody. The effect of IFN on the topography of H-2 determinants as measured by the blocking index was variable, depending upon the MCA-treated clone used and the genetic determinants of H-2 antigenic activity responding to the antisera used. Rosette-forming capacity with SRBCs differed between the two MCA-treated clones; one responded to IFN treatment by greater rosette formation; the other did not. Enhancement of H-2 antigen expression after IFN treatment apparently was the result of change in the spatial relationship of H-2 determinants on the cell surface rather than an actual increase in the number of H-2 antigenic receptors. (37 Refs)

41. AN EXTRA-NUCLEAR FUNCTION OF RETINOIC ACID (MEETING ABSTRACT)

Bolmer SD, Wolf G
Massachusetts Institute of Technology, Cambridge, MA, 02139
Fed Proc; 41(3):740 1982

Retinoids have long been known to inhibit the activity of phorbol esters in tumor promotion. In vitro studies have shown that phorbol esters cause cells to assume many, but not all, the characteristics of transformed cells. Among these are increased deoxyglucose uptake, induction of ornithine decarboxylase (ODC), and loss of fibronectin (FN). We investigated the effect of tetradecanyol phorbol acetate (TPA) and retinoic acid (RA) on enucleated cells. In normal Swiss 3T3 cells 10(-9)-10-6M TPA caused a dose dependent increase in both ODC activity and release of FN into the cell media. Cellular FN was labeled by incubating the cells in 3H-leucine for 4 hrs, before changing the media and adding TPA+/- RA. Cells treated with 10-6M TPA for 4 hrs lost nearly twice as much FN as control cells. In cells treated with 10-6M TPA, 10(-8)-10-6M RA inhibited stimulation of ODC and loss of FN so that at 10-6M RA, the FN in the media was nearly the same as in the media of the control cells. Next, 3H-leucine labeled cells were enucleated with cytochalasin B and centrifugation. The cells were better than 90% enucleated as shown by 3H-thymidine incorporation and Giemsa stain. When the enucleated cells were treated with 10-6M TPA, they released more than 2x as much FN as did control cells. RA (10-6M) reduced the loss of FN by greater than 30%. We conclude that TPA does not require the cell nucleus to induce release of FN and furthermore that RA does not require the cell nucleus to inhibit the action of the tumor promoter. (no Refs)

42. A MURINE MODEL SYSTEM FOR STUDYING THE MOLECULAR MECHANISM OF EPSTEIN-BARR VIRUS (EBV)-MEDIATED CELL TRANSFORMATION AND CARCINOGENESIS (MEETING ABSTRACT)

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Fed Proc; 41(3):688 1982

EBV can normally infect in vitro only human and marmoset B lymphocytes, leading to cell transformation without any primary viral reproductive cycle. Using our method of EBV receptor-implantation we demonstrated that any other cell which is artificially provided with EBV receptors can be infected by the virus. Here we show also that EBV receptor-implanted mouse lymphocytes are infectible by EBV, when using either the transforming B-95-8 (B-EBV) or non-transforming P3HR-1 (P-EBV) substrains of the virus. Unlike the natural host, mouse lymphocytes are not readily transformed by B-EBV. Instead, the cells support a full viral lytic cycle, resulting in the release of a new biologically active EBV isolate (M-EBV). Unlike the natural host, the EBV-infected mouse cells express the virus-determined early (EA) and virus capsid (VCA) antigens. Suprisingly, the EBV-nuclear antigen (EBNA) is barely detectable. This model system is used to test the hypothesis that the EBV-related oncogenic mechanism involves a virus-mediated increase in intracellular proteins, presumably as a complex between a virus coded 48,000 dalton component and a cell-coded 53,000 dalton component, which may block the viral lytic cycle and interfere with cell differentiation leading to transformation. (no Refs)

43. IN VITRO TRANSFORMATION BY AVIAN ERYTHROBLASTOSIS VIRUS RECRUITS CELLS OF ERYTHROID LINEAGE WITH VARYING DEGREE OF DIFFERENTIATION.

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Int J Cancer; 29(5):555-558 1982

We have previously shown that the AEV infection of leukosis-free chickens provokes an erythroleukemia in the infected birds, and that the target cell for virus transformation is most likely an early pro-erythroblast comparable to the BFU-E. The virus infection correlates with a block in differentiation which was studied at a specific cellular gene level, namely that of the globin genes. In live birds, the viral transformation has been found to affect the transcriptional activity of two out of three adult globin genes and the phenotypic expression of the third. Indeed, the alphaa gene that is transcribed is silent as well, since its transcription product is fully eliminated in the nucleus following an 'abortive processing'. Chick bone marrow cells can also be transformed in vitro by AEV in which case the virus recruits, as targets, cells of the erythroid lineage belonging to a wider spectrum and hence in varying degrees of differentiation. In contrast to the results obtained with in vivo transformed cells, molecular hybridization with globin cDNA probes showed that in the erythroblasts transformed in vitro under tissue culture conditions all the three adult globin genes are transcriptionally active. Judging from our present results, we may propose that AEV transformation in vitro does not shut off but only modulates the already functioning erythroid cell differentiation program. (14 Refs)

BIOCHEMICAL AND MOLECULAR BIOLOGICAL STUDIES OF TRANSFORMED PHENOTYPE

44. DNA METHYLATION IN MOUSE CELLS IN CULTURE AS MEASURED BY RESTRICTION ENZYMES.

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Biochim Biophys Acta; 697(1):53-59 1982

Methylation of DNA in normal mouse cultured 3T3 cells and in their virally or chemically transformed derivatives was studied. DNA methylation was studied by restriction with HpaII, MspI, or HpaII plus MspI. DNA from the chemically transformed cells was cleaved about twice as often with HpaII than was the DNA of normal and virally transformed cells. Digests with MspI and HpaII plus MspI were identical in all cell lines studied. Densitometry of the restriction patterns allowed an estimate of total DNA methylation from the wt av lengths. The chemically transformed cell line showed 25% reduction in methylation compared to the other cell lines. Southern blot hybridization using satellite DNA showed that these sequences followed a pattern of modification similar to that of total DNA. (Author abstract) (47 Refs)

45. HEPATITIS B VIRUS AND PRIMARY LIVER CANCER: DEMONSTRATION OF A CYTOPLASMIC TUMOR ANTIGEN IN THE TRANSFORMED HEPATOCYTE.

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C R Acad Sci [III] (Paris); 294(1):9-14 1982

The presence of tumor antigen was studied in human hepatoma cell line PLC/PRF/5 by indirect immunofluorescence and immunoperoxidase assay using antisera from 14 Senegalese patients with primary hepatocellular carcinomas. Ten of the 14 sera were HBs Ag-positive, 4/10 also HBe Ag-positive, 3/14 anti-HBsd antibody-positive and 1/14 anti-HBc antibody-positive. Twenty-two sera without hepatitis B virus markers from African Blood donors and from cancer patients were used as controls. Tumor antigen (HBV/T) was found in the cytoplasm of the human hepatoma cells. The same antigen was also detected in primary hepatocellular carcinoma tissues. The data obtained with serum and tissue controls indicate that the HBV/T Ag-anti-HBV/T system seems to be associated with the transformation of hepatocytes by hepatitis B virus. (15 Refs) (In FRE)

46. ANALYSIS OF THE TRANSPORT SYSTEM FOR INORGANIC ANIONS IN NORMAL AND TRANSFORMED HEPATOCYTES.

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J Biol Chem; 257(8):4381-4385 1982

The transport system for inorganic anions has been investigated in hepatocytes and hepatoma tissue culture cells. Sulfate transport in hepatocytes is temperature sensitive and occurs against an electrochemical gradient. Uptake was shown to occur by a sodium-dependent and a sodium-independent route with Km values of 2.3 and 33 mM and Vmax values of 2.1 and 10nmol/mg of protein/min, respectively. An analysis of the sodium dependency indicates a Hill coefficient of 1.05 suggesting an equimolar stoichiometry for sodium and sulfate transport. The transport of sulfate was decreased by metabolic and sodium transport inhibitors. Bicarbonate was shown to affect the transport of sulfate, where uptake was accelerated by intracellular bicarbonate and competitively inhibited by extracellular bicarbonate. In addition, sulfate efflux was stimulated by extracellular bicarbonate. These results suggest that bicarbonate is a substrate for the sulfate transport system and can accelerate uptake and efflux by an anion exchange mechanism. Inhibition of bicarbonate uptake by extracellular sulfate and by the anion transport inhibitor 4,4'-diisothiocyano-2,2'-stilbene disulfonate demonstrates that bicarbonate does not enter the cell exclusively by CO2 diffusion but can be transported in part as an anionic species. These results are consistent with its role in the sulfate-bicarbonate exchange system. This inorganic anion transport system was shown to be inhibited by approx 80% in hepatoma tissue culture cells where altered sodium dependency, Km, and Vmax values reflect possible alterations in the structure and/or membrane content of the carrier. (Author abstract) (30 Refs)

47. EFFECT OF HEPATOCYTE PROLIFERATION AND NEOPLASTIC TRANSFORMATION ON ALPHA-FETOPROTEIN (AFP) AND ALBUMIN (ALB) PRODUCTION PER CELL. INFLUENCE OF CELL SPECIALIZATION AND CELL SIZE.

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Oncodev Biol Med; 3(1):49-63 1982

Hepatocytes were isolated from 2-day regenerating livers of 21-day- and 12-wk-old rats, and the percentage of cells specialized in AFP and ALB production was evaluated using the reverse hemolytic plaque assay. In comparison to the data obtained with hepatocytes from non regenerating livers, the percentage of ALB producers was not significantly modified during the regenerating process; the percentage of AFP producers at 23 days of age went from a non detectable level to 5% while at 12 wk it remained at an extremely low value. Double identification of secreting hepatocytes further revealed that the re-occurring AFP producers were recruited among those already producing ALB. The isolated hepatocytes were also fractionated according to size by velocity sedimentation at 1 x g and the actual production rate of AFP and ALB was determined on a per cell or a per mg protein basis. Again, regeneration process did not alter the ALB production rate, whereas AFP became detectable only with hepatocytes from 23-day-old rats. The same approach was used to evaluate the relationship between AFP/ALB specialization versus cell size for Morris 7777 and 7795 and Novikoff hepatoma cells. The results showed that on a per mg basis, after correction for the percentage of specialized cells, Morris 7777 cells produced AFP at a rate comparable to that of the normal neonatal hepatocytes. Both Morris 7777 and 7795 hepatoma cells produced ALB at a low rate. Novikoff hepatoma cells produced no detectable amount of the two exportable proteins. The analysis by velocity sedimentation at 1 x g also revealed that the three hepatoma cell lines were essentially identical in size. They were found to be smaller than neonatal hepatocytes but comparable in size to hepatic epithelial cells that can be isolated from normal rats and propagated in culture. These results are discussed in terms of proposals suggesting that hepatic epithelial cells may correspond to precursors or stem cells of hepatocytes and to target cells during chemical hepatocarcinogenesis. (Author abstract) (56 Refs)

48. GROWTH INHIBITION (GI) OF UNDIFFERENTIATED LYMPHOMA (UL) CELLS BY SURFACE IGM MODULATION (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:1005 1982

We have initiated a series of studies to determine the effects of surface IgM modulation on the growth of human UL cell lines. IgM modulation was affected with low doses (7ug/ml) of anti-IgM (u specific). The majority (5/7) of the American UL cell lines showed major GI (53-94%) as a result of surface IgM modulation. GI (greater than 30%) was not detected in any African Burkitt's lymphoma cell lines (3), Epstein Barr Virus (EBV)-transformed cord blood lymphocyte lines (3), or other EBV-containing lymphoblastoid cell lines (2). American UL cell lines inhibited by anti-Igm treatment did not contain the EBV genome, whereas lines which displayed weak GI were EBV+. GI of the American UL cell lines was observed following treatment with antibodies directed against u-heavy chain or the specific light chain class (kappa) that each cell line displayed, however GI was not detected following exposure of the cells to F(ab)'2 fragments directed against IgM heavy chain or antisera against other cell surface determinants. GI occurred rapidly with detectable effects at 2-6 hours after exposure to antibodies and maximum inhibition of (3H)-thymidine incorporation at 24 to 48 hours after treatment. GI was not associated with marked cytotoxicity. We have previously hypothesized that the American UL cells represent immature B-lymphocytes. This GI effect may be related to the induction of tolerance in neonates by anti-IgM antisera. (no Refs)

49. CALMODULIN AND CA2+ IN NORMAL AND TRANSFORMED CELLS.

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Fed Proc; 41(7):2283-2288 1982

Numerous lines of evidence implicate calcium and calmodulin (CaM) as regulators of cell growth and functional differentiation. In light of this evidence, several studies of the possible involvement of the CaM system in cellular transformation by RNA and DNA tumor viruses have been carried out. This paper summarizes the evidence linking calcium and CaM to the regulation of cell growth and critically examines the evidence that increases in CaM levels occur in transformed versus normal cells. A nontraumatic method for synchronizing both normal and transformed chick fibroblasts is presented. This method is utilized in a comparison of CaM levels throughout the cell cycle of Rous sarcoma virus transformed and normal chick embryo fibroblasts. These studies best support the hypothesis that the observed differences in CaM levels between transformed and normal cultures under optimal growth conditions may largely reflect differences in the proportion of cells in a dividing versus a nondividing state. (Author abstract) (41 Refs)

50. ORNITHINE DECARBOXYLASE INDUCTION AND THE CYTOSKELETON IN NORMAL AND TRANSFORMED CELLS.

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J Cell Physiol; 111(2):133-139 1982

Ornithine decarboxylase (ODC) induction of normal human skin fibroblasts by colchicine (COL) and other cytoskeletal disorganizing agents was compared to that of HeLa and transformed CHO-K1 cells. Treatment with fresh medium alone was sufficient to release a large fraction of the G1 block in HeLa cells, whereas serum was required to release normal fibroblasts from G1 block. DNA synthesis in the growth arrested cells was minimal and release from G1 block was followed by initiation of ODC synthesis and subsequently of DNA synthesis in both cell lines. Induction of ODC by medium change was completely prevented in both cell lines by addition of 10 ug/ml actinomycin D (ACTD) or 25 ug/m cycloheximide (CYH). The fact that ODC activity in cells released from G1 block revealed rising and falling phases indicated that both activating and inactivating processes were involved. While increasing COL concentrations ODC induction decreased in normal fibroblasts. The curve for HeLa cells was biphasic. Vinblastine produced effects similar to those of COL. If inhibitory drugs were not added until several hr after medium change, CYH alone produced a steadily diminishing ODC activity in both cell lines. In the absence of protein synthesis, COL did not contribute any additional effect to the enzyme inactivation process. The inhibitory action of COL was probably exerted on prevention of protein synthesis rather than inactivation of already synthesized enzyme. The CHO-K1 cell line resembled HeLa cells in all respects. (30 Refs)

51. TRANSFORMATION BY AVIAN SARCOMA VIRUSES LEADS TO PHOSPHORYLATION OF MULTIPLE CELLULAR PROTEINS ON TYROSINE RESIDUES.

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J Virol; 42(2):742-747 1982

Phosphoamino acid compositions were determined for 10 size classes of cellular proteins, separated by electrophoresis through one-dimensional sodium dodecyl sulfate-polyacrylamide gels. Phosphotyrosine-containing proteins were observed in uninfected chicken embryo fibroblasts in every size class analyzed, ranging from approx 20,000 to greater than 200,000 daltons. Transformation of chicken embryo fibroblasts by Rous sarcoma virus or PRC II avian sarcoma virus led to increases in phosphorylation of proteins at tyrosine residues in all of these size classes. A large fraction of the phosphotyrosine-containing protein molecules observed in Rous sarcoma virus-transformed cells was larger than 100,000 daltons with a second broad peak in the 35,000-to 60,000-dalton range. This study suggests that there are a number of substrates of viral or cellular tyrosine-specific protein kinases, which have not yet been identified by other methods. (Author abstract) (31 Refs)

52. RETINOIC ACID BINDING PROTEIN IN NORMAL AND NEOPLASTIC RAT PROSTATE.

Gesell MS, Brandes MJ, Arnold EA, Isaacs JT, Ueda H, Millan JC, Brandes D

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Prostate; 3(2):131-138 1982

Cytosolic retinoic acid-binding protein (cRABP) was detected, using sucrose density gradient centrifugation, in four sublines of the Dunning R 3327 transplantable prostatic carcinoma and in the normal lateral prostate of the Fisher-Copenhagen F1 rat; cRABP was not detected in the dorsal lobes (the tissue of origin of R 3327 in a Copenhagen rat) or ventral prostate. The presence of cRABP in all four R 3327 tumor sublines, which differ in their degree of differentiation and hormone responsiveness, suggests that cRAPB may be a marker of malignant transformation similar to other oncofetal proteins in human and animal tumors. (40 Refs)

53. SIMILAR GLYCOPEPTIDES IN NORMAL CHONDROBLASTS AND IN ROUS SARCOMA VIRUS-TRANSFORMED FIBROBLASTS.

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J Biol Chem; 257(8):4463-4468 1982

Fucose-labeled glycopeptides were isolated from the glycoproteins of normal chick embryo chondroblasts grown in monolayer cultures or in suspension. Analysis by chromatography on Sephadex G-50 columns revealed that a large proportion of these glycopeptides co-migrated with the large mol wt glycopeptides (Group A) reported in numerous types of tumorigenic cells. the proportion of Group A glycopeptides in normal chondroblasts was essentially identical with that found in chick embryo skin fibroblasts transformed by a temperature-sensitive mutant (ts-LA24A) of Rous sarcoma virus and grown at the permissive temperature. When chondroblasts transformed with ts-LA24A were grown at either the permissive or the nonpermissive temperature, no changes were observed in the overall pattern of glycopeptide synthesis or in the amount of Group A glycopeptides synthesized. Furthermore, when the various glycopeptides synthesized by normal and transformed chondroblasts were compared by concanavalin A-Sepharose affinity chromatography and DEAE-Sephadex ion exchange chromatography, no significant differences were found. The unusually high level of Group A glycopeptides found in monolayer or in suspension cultures of normal chondroblasts appears to be under environmental control. Thus, normal chondroblasts in vivo, as well as in organ culture, did not synthesize the large proportion of Group A glycopeptides, and the overall pattern on Sephadex G-50 column chromatography was indistinguishable from that of normal skin fibroblasts. We conclude that (1) normal chondroblasts in monolayer or suspension cultures can be induced to synthesize a class of molecules characteristic of transformed cells, and (2) though the synthesis of these glycopeptides may not be a prominent part of the normal in vivo biosynthetic program of chondroblasts, their synthesis in vitro probably reflects a response or adaptation to differences in their microenvironment. (Author abstract) (31 Refs)

54. DIFFERENCES IN GROWTH REGULATION OF NORMAL AND TUMOR CELLS (MEETING ABSTRACT)

Pardee AB, Campisi J, Croy RG

Sidney Farber Cancer Institute, Boston, MA

Conference on Cell Proliferation, Cancer and Cancer Therapy, February 17-19, 1982, New York, New York New York Academy of Sciences; :A13 1982

Normal cells cannot initiate DNA synthesis yet complete their division cycle under inadequate external conditions. The sensitive biochemical event is proposed to be accumulation of protein which in adequate amounts permits entry into S phase, after about 2 hr, and completion of the cycle. Instability of the protein (half life about 2.5 hr) creates a dynamic state so that accumulation depends on rates of both synthesis and degradation. Neoplastic cells may show poorly regulated growth by synthesizing more of this protein or degrading it less rapidly, under conditions that limit normal cells' growth. Overproduction can result from more copies of structural gene per cell, adjacent promoter of high activity, or autoproduction of growth factors. Less rapid degradation could result from less protease activity, or from stabilizing modifications of the protein. Alterations of protein metabolism by these mechanisms have been described. Thus, diverse transforming agents acting via different mechanisms could affect a common regulatory process leading to neoplasia. (no Refs)

CELL SURFACE PHENOMENA OF TRANSFORMATION

55. EARLY ANTIGENIC CHANGES INDUCED BY 3-METHYLCHOLANTHRENE (3MCA) ASSOCIATED WITH CARCINOGENESIS IN SYRIAN HAMSTER CELL (MEETING ABSTRACT)

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Fed Proc; 41(3):414 1982

The character of cell surface antigens in carcinogenesis was examined using hamster antisera to approximately 15 days gestation hamster embryo cells treated for 18 hours with 10 ug/ml 3MCA (test sera) and 46 cell lines independently isolated from colonies of 3MCA in vitro transformed hamster cells growing in agar. Test sera binding to target cells was quantitated with 125I-labeled rabbit anti-hamster IgG and compared to that of control sera produced to non-carcinogen (solvent) treated embryo cells. A normal distribution of antigenic cell surface changes was seen on the 46 cell lines; 9 (20%) bound the test sera at least 2 SE greater than the binding of the control sera, 33 (72%) showed no significant differences in binding and the remaining 4 bound more control sera than test sera. Absorption of the test sera with the cell lines and cells from embryos of 10 days gestation indicated that the determinant(s) recognized were common and also expressed on fetal cells. Thus cell surface changes induced by 3MCA treatment can include the loss, decrease or increased expression of normal antigen(s) and possibly de novo antigen synthesis. The occurrence of early and persistent immunogenic changes in cell surface components during carcinogenesis presents the opportunity for in vivo host interactions modulating the carcinogenic process. (no Refs)

56. ANTISERA AGAINST TUMOR-ASSOCIATED SURFACE ANTIGENS ON METHYLCHOLANTHRENE-INDUCED SARCOMAS BIND TC T CELL REGULATORY MOLECULES (MEETING ABSTRACT)

Flood P, Yamauchi K, DeLeo A, Old L, Gershon R
Yale University School of Medicine, New Haven, CT, 06510
Fed Proc; 41(3):722 1982

A cell-free product secreted by Lyt 1+,2-I-J+ cells (Ly 1 TsiF) acts in combination with Lyt 1+,2+ I-J+ cells to induce suppressor cell activity. Antisera raised in syngeneic or semi-syngeneic F1 Balb/c mice to antigens on methylcholanthrene (MC)-induced fibrosarcomas block this Igh-linked genetically-restricted T-T cell interaction. The antisera only blocked when either the Ly 1 TsiF or its acceptor cells shared the Igh gene polymorphism with Balb/c mice. Additionally, only Ly 1 TsiF from Igha strain mice were bound by the anti-MC tumor immunosorbent column. Material eluted from the anti-MC column had no suppressive activity and did not bind antigen, but suppressive activity was restored when mixed with any Ly 1 TsiF filtrate from an anti-I-J column. Cross clearing experiments indicated the molecule bound by the anti-MC tumor immunosorbent was the I-J+ non-antigen binding molecule which imparts VH restriction to the Ly1 TsiF. These results show MC-induced sarcomas express cell surface structures that are serologically related to T cell interaction structures and antibodies against them can be utilized to identify T cell subsets and their biologically active molecules. (no Refs)

57. SEROLOGICAL ANALYSIS OF CELL SURFACE ANTIGENS ON METHYLCHOLANTHRENE-INDUCED MOUSE SARCOMAS WITH ANTISERA PRODUCED AGAINST THE TUMORS.

Tanimoto M, Takahashi T, Nishizuka Y
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Gan; 73(2):184-192 1982

Out of nine cell lines from methylcholanthrene-induced fibrosarcomas in BALB/c, four lines without expression of murine leukemia virus (MuLV) were selected for immunization of three different F1 hybrids with mitomycin C-treated in vivo sarcoma cells. Antibody activity was tested by immune adherence (IA) and protein A (PA) assays after the eighth immunization. Two sarcomas, CMC-11 and CMC-12, produced antibodies detectable by IA in (BALB/c x C3H/He)F1, but no antibodies were detected by PA. (BALB/c x C3H/He)F1 anti-CMC-11 was tested against CMC-11 and three other MuLV-sarcomas as well as against the skin fibroblast (C-11) from a BALB/c mouse, in which the primary CMC-11 sarcoma was induced. CMC-11 line reacted up to 1/80, but other lines were weakly positive or negative. Absorption analysis showed that the antigen defined by anti-CMC-11 was present on CMC-11 as well as on many other sarcoma cell lines, but not on BALB/c thymocytes and spleen cells, nor on leukemia and myeloma cells. Among five fibroblast cultures tested, C-14 showed complete absorption. It seems significant that only C-14 produced tumor nodules in BALB/c mice, in contrast to four other fibroblast cultures. This suggested that this antibody was directed against antigens present on transformed fibroblasts and sarcoma cells. The specificity of (BALB/c x C3H/He)F1 anti-CMC-12 serum indicated that this antiserum also seemed to detect transformation-related antigens, although it showed a broader specificity with regard to the tissue representation detected. (Author abstract) (29 Refs)

58. PURIFICATION OF A NATIVE MEMBRANE-ASSOCIATED ADENOVIRUS TUMOR ANTIGEN.

Persson H, Katze MG, Philipson L
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J Virol; 42(3):905-917 1982

A 15,000-dalton protein was purified from HeLa cells infected with adenovirus Type 2. Proteins solubilized from a membrane fraction of lytically infected cells was used as the starting material for purification. Subsequent purification steps involved lentil-lectin, phosphocellulose, hydroxyapatite, DEAE-cellulose, and aminohexyl-Sepharose chromatographies. A monospecific antiserum, raised against the purified protein, immunoprecipitated a 15,000-dalton protein encoded in early-region E1B (E1B/15K protein) of the adenovirus Type 2 DNA. Tryptic finger print analysis revealed that the purified protein was identical to the E1B/15K protein encoded in the transforming part of the viral genome. The antiserum immunoprecipitated the E1B/15K protein from a variety of viral transformed cell lines isolated from humans, rats, or hamsters. The E1B/15K protein was associated with the membrane fraction of both lytically and virus-transformed cell lines and could only be released by detergent treatment. Furthermore, an 11,000-to 12,000-dalton protein that could be precipitated with the anti-E1B/15K serum was recovered from membranes treated with trypsin or proteinase K, suggesting that a major part of the E1B/15K protein is protected in membrane vesicles. Translation of early viral mRNA in a cell-free system, supplemented with rough microsomes, showed that this protein was associated with the membrane fraction also in vitro. (Author abstract) (47 Refs)

59. LOSS OF DIFFERENT PERICELLULAR MATRIX COMPONENTS OF RAT CELLS TRANSFORMED WITH A T-CLASS TS MUTANT OF ROUS SARCOMA VIRUS.

Alitalo K, Keski-Oja J, Hedman K, Vaheri A
Dept. Microbiology and Immunology, Sch. Medicine, Univ. California, San Francisco, CA, 94143
Virology; 119(2):347-357 1982

Rat cells transformed by the T-class ts mutant LA339 derived from SSV B77 (2R cells) and the parental nontransformed Rat-1 cells were analyzed for the production and deposition of pericellular matrix components as a function of growth temperature. The cells were incubated at the permissive (35 C) and nonpermissive (39.5 C) temperatures for transformation and the collagenous and noncollagenous (fibronectin and laminin) matrix proteins were studied by polypeptide analysis of the metabolically labeled cells and their culture media. Immunofluorescence analysis of the pericellular matrix starucstures was performed using specific antibodies against laminin, fibronectin, and heparan sulfate proteoglycan. At 39.5 C dense pericellular matrices were detected in both 2R and Rat-1 cell layers, whereas at 35 C the 2R cells lost their pericellular matrix structures. The cells continued to synthesize and secrete fibronectin, laminin, and heparan sulfate proteoglycan as well as slightly reduced amounts of procollagen into the culture medium but failed to deposit them in a matrix form. Another major temperature-sensitive difference in the secreted polypeptides was the production by the 2R cells at 35 C of a 56,000-dalton protein, similar to that reported in other transformed cell cultures. The present findings indicate that the transformed rat 2R cells lose, upon activity of the pp60src, their capacity to deposit the synthesized matrix components into pericellular structures. (Author abstract) (48 Refs)

60. ALTERATIONS IN PROTEIN AND GLYCOPROTEIN COMPOSITION OF RAT EMBRYO FIBROBLASTS TRANSFORMED BY HERPES SIMPLEX VIRUS TYPE 2.

Rosnowski W, Blaszczyk M, Darai G, Munk K
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Oncology; 39(4):222-227 1982

Total and superficially exposed plasma membrane components of tumorigenic herpes-simplex-virus(HSV)-transformed fibroblasts were studied. As a result of oncogenic HSV transformation, a significant decrease of polypeptides 230,000, 180,000, 56,000 and 43,000 daltons was found. These changes were accompanied by a significant increase in superficial exposition of several sialopeptides and two peptides of 30,000 and 15,000 daltons. It was suggested that these two peptides may represent virus-coded components of HSV-transformed fibroblasts. The present results indicate that the HSV-transformed tumorigenic cell clone meets all previously described criteria for oncogenically transformed cells. (Author abstract) (38 Refs)

61. THE TRANSFORMATION-SENSITIVE GLYCOPROTEIN LAMININ IS AN AGGLUTININ (MEETING ABSTRACT)

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Med Pediatr Oncol; 10(1):100 1982

Laminin is a high molecular weight glycoprotein involved in the adhesion of a variety of epithelial cells to type IV collagen of basement membranes. The protein consists of at least two polypeptide chains of 220,000 and 440,000 daltons joined to each other by disulfide bonds. Laminin is found to agglutinate formalinized sheep erythrocytes at protein concentrations of under 1 ug/ml. This finding provides a simple model system for analyzing laminin-mediated adhesion and for searching for its cell surface receptor in competitive inhibition experiments. Laminin-mediated hemagglutination is markedly inhibited by highly negatively charged phospholipids and by purified solubilized gangliosides. The inhibition is dose-dependent and competitive; hemagglutination by 4 ug/ml laminin is half-maximally inhibited by less than 1 uM phosphatidic acid and by less than 5 uM gangliosides. The order of inhibition by gangliosides is GD1a greater than GT1b greater than GM1. A series of other lipids, ganglioside constituents, monosaccharides, glycosaminoglycans, and glycoproteins are either less effective or without detectable competitive inhibitory activity. These results suggest that hypothesis that laminin mediates normal epithelial cell adhesion by binding to a cell-surface receptor that may contain a negatively charged cell-surface component such as a ganglioside or another highly charged lipid. (no Refs)

62. DIFFERENTIAL ANTIGENIC EXPRESSION OF THE DBA/2 LYMPHOMA L1210 AND ITS SUBLINE CELLS AND CROSSREACTIVITY WITH C3H ANTIBODY (MEETING ABSTRACT)

Rapp L, Fuji H
Roswell Park Memorial Institute, 666 Elm Street, Buffalo, NY, 14263
Proc Am Assoc Cancer Res; 23:1068 1982

The nature of antigenic expression on the DBA/2 lymphoma, L1210, and three highly immunogenic drug-resistant sublines was investigated using syngeneic hybridoma antibodies produced by the fusion of spleen cells from DBA/2 mice immunized with irradiated L1210 or L1210 subline cells and a non-Ig secreting BALB/c myeloma. Monoclonal antibodies from either the anti-L1210 or the anti-L1210 subline hybridomas reacted more strongly with L1210 subline cells than the parent L1210 cells in complement-dependent cytotoxicity experiments. These antibodies were absorbed more efficiently with the subline cells than the parent cells. Most syngeneic and allogeneic control lymphomas, including those induced by murine-leukemia viruses, did not demonstrate significant reaction with the antibody except for the DBA/2 lymphoma L5178Y, which showed a weak reaction. However, various degrees of crossreactivity were observed between the monoclonal antibodies and several spontaneous C3H/St mammary tumors (MT) in absorption tests. This crossreactivity was also demonstrated by immunofluorescence staining of MT tissue sections and complement-dependent cytotoxicity on cells of a MT transformed into ascites form. These results indicate that the drug-resistant L1210 sublines express an increased amount of the monoclonal antibody-defined antigens; these antigens may resemble the mammary leukemia (ML) antigen described by Stuck, et al. (2 Refs)

63. NEOANTIGEN EXPRESSION IN CHEMICAL CARCINOGENESIS.

Baldwin RW, Price M

Cancer Res. Campaign Laboratories, Univ. Nottingham, Nottingham, England

Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Neoantigens have been found on tumors which were chemically induced by polycyclic hydrocarbons, by aminoazo dyes, by aromatic amines, by alkylnitrosamines, and by hydrazines. Several findings are consistent with the view that tumor-associated antigens on chemically induced tumors are expressed on integral membrane proteins or glycoproteins. Attempts to develop cell-free radioimmunoassays for these antigens have generally been unsuccessful. One of the major problems has been to retain the capacity of the radiolabeled antigens to rebind with antibodies in syngeneic immune sera. The significance of the possible relationships between tumor-associated neoantigens and products of major histocompatibility complex needs to be further evaluated. Oncodevelopmental antigens appear to be associated with numerous types of chemically induced tumors, and thus they should be regarded as valuable potential markers for studying transformation-related events. Three possible pathways leading to neoantigen expression include their appearance as a consequence of early interactions of carcinogen with target cells, their expression which only occurs once the initiated cell is converted to the preneoplastic cell, and their expression at the stage when malignant cell clones develop. (328 Refs)

MORPHOLOGICAL AND OTHER BIOLOGICAL ASPECTS OF ONCOGENIC TRANSFORMATION

64. HETEROGENEITY OF TUMORIGENICITY PHENOTYPE IN MURINE TUMORS. CHARACTERIZATION OF TUMOR CLONES ISOLATED FROM PRIMARY 3-METHYLCHOLANTHRENE-INDUCED FIBROSARCOMAS.

Schmitt M, Daynes RA
(c/o Daynes) Dept. Pathology, Univ. Utah Medical Center, Salt Lake City, UT, 84132
Transplantation; 33(4):387-392 1982

In this study we have characterized three series of clonal populations isolated from primary murine fibrosarcomas induced with three different doses of the chemical carcinogen, 3-methylcholanthrene (3-MCA). Clones were evaluated for their in vivo growth rates after transplantation into normal syngeneic animals, and for immunological cross-protection toward clones derived from the same tumor. A pattern of reactivity emerged from these studies which supports, at the single-cell level, existing theories regarding the correlation between the inducing dose of chemical carcinogen and the antigenicity of the resulting tumors. Clones from tumors induced with 10 mg of 3-MCA were found to be less tumorigenic than clones from tumors induced with 5 mg of 3-MCA. The 5-mg clones were in turn less tumorigenic than the 1-mg clones, all of which grew rapidly in normal animals. Related clones from each tumor were found for the most part to be immunologically noncross-reactive with other clones from the same tumor, suggesting that subpopulations of tumor cells expressing different tumor-specific transplantation antigens (TSTAs) may reside within single primary tumors. We have used these observations to formulate an hypothesis for the origin of antigenic heterogeneity in 3-MCA-induced tumors and as the basis for a discussion of the relationship between cell transformation and the appearance at the cell surface of tumor-specific transplantation antigens. (Author abstract) (19 Refs)

65. TUMORIGENICITY OF PARTIAL TRANSFORMATION MUTANTS OF ROUS SARCOMA VIRUS.

Kahn P, Nakamura K, Shin S, Smith RE, Weber MJ
(c/o Weber) Dept. Microbiology, Univ. Illinois, Urbana, IL, 68103
J Virol; 42(2):602-611 1982

Chicken embryo cells infected with partial transformation mutants of Rous sarcoma virus were tested for tumor-forming ability in chickens and in nude mice. Cells transformed by each of these partial transformation mutants display different combinations of transformation parameters. They therefore present a potentially favorable system for analyzing which properties of transformed cells are necessary for tumor formation. We found that the relative tumorigenicity of the virus mutants was generally similar in chickens and in nude mice, except that certain temperature-conditional mutants appeared to be sensitive to the differences in both temperature of the two experimental animals. (The body temperature of nude mice is 4 to 5 C lower than that of chickens). Thus, the nude mouse appears to be a suitable system for testing the tumorigenicity of transformed chicken cells. Because mice are nonpermissive for Rous sarcoma virus infection and replication, it was possible to recover the transformed chicken cells from the tumors in this host and to determine what phenotypic changes they had undergone during tumor development. We also examined the relationship between various cellular properties of the virus-infected chicken cells in vitro and their tumorigenicity in nude mice. The combined results of these two studies indicated that anchorage independence and plasminogen activator production were highly correlated with the tumor-forming ability of these cells, whereas loss of fibronectin did not correlate with tumorigenicity. Furthermore, the inability of the least tumorigenic virus mutant to stimulate the phosphorylation of a 36,000-Mr target of pp60src raises the possibility that the 36,000-Mr protein plays a role in tumor formation. (Author abstract) (31 Refs)

66. SENSITIVITY OF ADENOVIRUS-TRANSFORMED CELL LINES OF DIFFERENT TUMORIGENICITY TO KILLING BY SYNGENEIC NATURAL KILLER CELLS (MEETING ABSTRACT)

Raska K, Gallimore PH
Department of Pathology, CMDNJ-Rutgers Medical School, Piscataway, NJ, 08854
Proc Am Assoc Cancer Res; 23:949 1982

In this study, the tumorigenic potentials of six adenovirus-transformed LIS cell lines were studied in syngeneic rats. The cells used are well characterized as to the content and expression of the adenovirus genome. The in vivo tumorigenic potential of these individual cell lines in LIS rats varied from nontumorigenicity in immunosuppressed newborn animals to high tumorigenicity in untreated newborn and weanling rats. This different capacity to induce tumors does not correlate with a number of in vitro properties of these cell lines, such as growth saturation density, decreased doubling time, increased fibrinolytic activity or anchorage independent growth. Similarly, the ability of these cell lines to elicit the cytolytic T cell response in syngeneic LIS rats also does not universally correlate with their tumorigenic potential. When the capacity to induce tumors in vivo, however, was compared with the sensitivity of these transformed cell lines to in vitro killing by natural killer (NK) cells in syngeneic lymphoid cell preparations, an inverse relation was found between these two parameters. In parallel experiments no significant differences were detected in the sensitivity of these cell lines to in vitro killing with syngeneic secondary cytolytic T cells. (no Refs)

67. ALTERED REGULATION OF PROLIFERATION IN TRANSFORMED LIVER EPITHELIAL CELLS (MEETING ABSTRACT)

McMahon JB, Iype PT
Chemical Carcinogenesis Program, National Cancer Institute-Frederick Cancer Research Facility, Frederick, MD, 21701
Conference on Cell Proliferation, Cancer and Cancer Therapy, February 17-19, 1982, New York, New York New York Academy of Sciences; :AP-8 1982

A quantitative colony assay which differentiates between cytotoxic or cytostatic (reversible) actions of test chemicals, was used to investigate the effect of factors isolated from adult rat liver. A partially purified fraction prepared by alcohol precipitation, ultrafiltration and Sephadex G-25 chromatography was found to show reversible inhibition of proliferation in non-malignant liver epithelial cell lines, but not in hepatoma or transformed liver cell lines. This fraction was purified to a homogeneous protein by additional DEAE (diethylaminoethyl) cellulose chromatography and/or anion exchange HPLC (high pressure liquid chromatography). The homogeneous protein also showed specificity towards non-malignant liver epithelial cells and is defined as a hepatic proliferation regulator (HPR). One of the early changes seen in a normal liver cell line treated with aflatoxin B1 was the loss of response towards HPR, which was followed by the expression of other transformation markers. HPR has a molecular weight of 26,000, and an isoelectric point of 4.65. Other physicochemical properties of HPR and its mode of action are being investigated. (no Refs)

ASSAYS OF ONCOGENIC TRANSFORMATION

68. IMPROVED TRANSFORMATION OF C3H10T1/2CL8 CELLS BY DIRECT- AND INDIRECT-ACTING CARCINOGENS.

Nesnow S, Garland H, Curtis G
Genetic Toxicology Div., Health Effects Res. Lab., United States Environmental Protection Agency, Research Triangle Park, NC, 27711
Carcinogenesis; 3(4):377-380 1982

Oncogenic transformation of C3H10T1/2CL8 cells was improved by treating the cells 5 days after seeding. Benzo[a]pyrene-induced transformation was increased 3.5-fold by this method, compared with treating the cells 1 day after seeding. N-Methyl-N'-nitro-N-nitrosoguanidine, which does not transform asynchronous cultures of C3H10T1/2CL8 cells when administered 1 day after seeding, produced an average of one focus/dish, with 61% of the dishes exhibiting foci, when administered 5 days after seeding. Propane sultone and aflatoxin B1 also produced marked transformation responses when administered 5 days after seeding. However, 4-dimethylaminoazobenzene did not induce transformation when administered either 1 day or 5 days after seeding. With all chemicals examined, clonal cytotoxicity was reduced when they were administered 5 days after seeding. These results indicate the utility of this new procedure for the qualitative analysis of the transforming ability of chemicals. (Author abstract) (28 Refs)

69. INITIATION OF C3H/10T1/2 CELL TRANSFORMATION BY N-METHYL-N'-NITRO-N-NITROSOGUANIDINE AND AFLATOXIN B1.

Boreiko CJ, Ragan DL, Abernethy DJ, Frazelle JH
Chemical Industry Inst. Toxicology, P.O. Box 12137, Research Triangle Park, NC, 27709
Carcinogenesis; 3(4):391-395 1982

The utility of C3H/10T1/2 mouse embryo fibroblasts for the detection of carcinogenic substances has been limited by their apparent insensitivity to the oncogenic effects of direct-acting alkylating agents such as N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and procarcinogens such as aflatoxin B1 (AfB1). Because the process of C3H/10T1/2 transformation can be observed to proceed through discrete stages of initiation and promotion, we have considered the possibility that MNNG and AfB1 may only initiate C3H/10T1/2 transformation. Treatment of asynchronous C3H/10T1/2 cells with MNNG or AfB1 alone generally produced few transformed foci. If MNNG or AfB1 treatment was followed by the exposure of cells to the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA), numerous transformed foci were produced. Phorbol did not enhance transformation by either substance. MNNG and AfB1 thus appear to be initiating agents for transformation. TPA also enhanced the transformation of C3H/10T1/2 cells by low doses of 3-methylcholanthrene (3-MCA), but transformation by high concentrations of 3-MCA was inhibited by the presence of TPA. These studies suggest that the sensitivity of the C3H/10T1/2 transformation system to potential carcinogens can be dramatically heightened if the bioassay is conducted in the presence and absence of TPA. (Author abstract) (37 Refs)

70. GENETIC DISTINCTION BETWEEN NEOPLASTIC GROWTH OF MAMMARY EPITHELIUM AND GROWTH IN 'TUMOR STEM CELL' ASSAYS (MEETING ABSTRACT)

Stanley WS, Montgomery J, Soule HD, McGrath CM
Michigan Cancer Foundation, Detroit, MI, 48201
Proc Am Assoc Cancer Res; 23:914 1982

Growth of solid tumor cells in agar or methylcellulose (MC) suspension is commonly used as a selective indicator for behavior of tumor 'stem cells'. The use of suspension cultures in 'stem cell assays' implies that controls for tumorigenic growth and growth in suspension are identical or very similar. We brought this idea in mammary cancer into question by demonstrating 1) that mammary cells cloned in MC failed to grow as tumors; and 2) tumorigenic cells cloned on solid substrates failed to grow in MC. We approached the problem further using somatic cell genetics. We found that the tumorigenic phenotype of a mouse mammary cell line (66CL) was expressed as a recessive trait (ie was suppressed) in intraspecies hybrids formed with normal lymphocytes and mammary cells. Fusions of 66CL cells with other tumorigenic cells gave evidence that the recessive lesions were allelic and that suppression of tumorigenicity was not due to host/cell incompatability factors. Hybrid clones suppressed for tumorigenicity nonetheless readily formed colonies in MC. Thus growth in MC was dominantly expressed and not coordinately suppressed with tumorigenicity. No hybrid clones exhibited a hyperplastic or precancerous phenotype. These data suggest that the genetic controls governing tumorigenicity in different tumor cells is the same but separate from controls governing growth in MC. Thus, growth in MC is not likely to be a selective condition for tumorigenic mammary 'stem cells'. Expression of tumorigenicity as a recessive trait is compatible with the two-step theory of transformation, though acquired ability to grow in MC suspension does not coincide with either precancerous or cancerous transformation. (no Refs)

GENERAL REVIEWS AND OTHER RELATED STUDIES

71. REGULATION OF GENE EXPRESSION IN NORMAL AND NEOPLASTIC CELLS. A REVIEW.

Hochhauser SJ, Stein GS, Stein JL
Dept. Biochemistry and Molecular Biology, Univ. Florida, Coll. Medicine, Gainsville, FL, 32610
Pathobiol Annu; 11:1-29 1981

Properties of the eukaryotic genome are discussed focusing on those aspects which have a direct bearing on organization, structure, and function. The levels at which gene expression is regulated and approaches that are being taken to examine control of transcription and subsequent processing and translation of gene transcripts are reviewed. The nature of gene expression in aberrant biological situations are assessed with the objective of defining possible molecular lesions. Enzyme components of nonhistone chromosomal proteins and differences between transformed or tumorigenic and untransformed cells are summarized. (352 Refs)

72. HOW DO PAPOVA VIRUSES PERSIST IN THEIR HOSTS?

Griffin BE
Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Symp Soc Gen Microbiol; 33:227-247 1982

Persistence of papova viruses; molecular organization of polyoma virus, simian virus 40 (SV40), and BK virus; transformation by polyoma virus and SV40; and persistence of viral sequences within transformed cells are reviewed. When considering the viral sequences retained within cell transformed polyoma virus and SV40, the main difference is that for maintenance of the transformed state, the entire 'early' region of SV40 appears to be required whereas with polyoma virus such is not the case. Similarities that emerge are those reflecting the presence of viral genomes within transformed cells, tandem arrays of viral sequences, and a general lack of specificity in the integration sites between viral and host cell DNA. (64 Refs)

73. THE PERSISTENCE OF RETROVIRUSES.

Weiss RA
Chester Beatty Res. Inst., Fulham Road, London SW3 6JB, England
Symp Soc Gen Microbiol; 33:267-288 1982

Persistence of retroviruses (RV) in host populations (horizontal and vertical transmission; xenotropic endogenous viruses; interspecies transmission of RV; inheritance, expression, and possible functions of endogenous viral genes), antigen shift and drift, pathogenesis (apathogenic infections, acute neoplasms, slow neoplasms, auto-immune disease and anemia, neurological disease, and RV and human disease) are reviewed. RV are unique in their replicative cycle and perhaps in the most intimate form of viral persistence as host Mendelian traits. The viral oncogenes give insight into normal cell regulation and differentiation, and its perversion as cancer. (70 Refs)

74. ROLE OF VIRUSES IN THE INDUCTION OF PRIMARY INTRACRANIAL TUMORS.

Walsh JW, Zimmer SG, Perdue ML
Div. Neurosurgery, Univ. Kentucky Medical Center, 800 Rose St., Lexington, KY, 40536
Neurosurgery; 10(5):643-662 1982

The literature on viral induction of intracranial tumors is reviewed, with special emphasis on the papovaviruses of the simian virus (SV)40 group. Discussion includes oncogenic studies in vivo and in vitro, the molecular basis for infection and transformation, and evidence that the papovavirus may cause human intracranial tumors. The latter was partly obtained from studies on children inoculated with live polio virus contaminated with SV40 who developed an excess of tumors, including intracranial tumors. (188 Refs)

75. FORM AND FUNCTION OF RETROVIRAL PROVIRUSES.

Varmus HE
Dept. Microbiology and Immunology, Univ. California, San Francisco, CA, 94143
Science; 216(4548):812-820 1982

Retroviruses have proved to be useful reagents for studying genetic and epigenetic (such as regulatory) changes in eukaryotic cells, for assessing functional and structural relationships between transposable genetic elements, for inducing insertional mutations, including some important in oncogenesis, and for transporting genes into eukaryotic cells, either after natural transduction of putative cellular oncogenes or after experimental construction of recombinant viruses. Many of these properties of retroviruses depend on their capacity to establish a DNA (proviral) form of their RNA genomes as a stable component of host chromosomes, in either somatic or germinal cells. (Author abstract) (114 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. MICROWAVE HEATING ENHANCES THE MIGRATION OF PLASTICIZERS OUT OF PLASTICS.
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3. NITROSAMINES.
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4. EXPERIMENTAL TUMORS OF THE PERIPHERAL NERVOUS SYSTEM.
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6. DIETHYLSTILBESTROL: EFFECT OF IN UTERO EXPOSURE.
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10. MUTAGENS, CARCINOGENS, AND TUMOR PROMOTERS IN OUR DAILY FOOD.
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12. VARIATIONS AMONG SPECIES AND CELL TYPES IN THE EFFECTS OF CAFFEINE ON MUTAGEN-INDUCED CYTOTOXICITY AND POSTREPLICATION REPAIR OF DNA.
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Richardson BJ, Waid JS
Marine Science Lab., Ministry for Conservation - Victoria, P.O. Box 114, Queenscliff, Victoria 3225, Australia
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Brandt L
Onkologiska kliniken, Lasarettet, Lund, Sweden
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23. ENVIRONMENTAL FACTORS AND MALIGNANT HEMATOLOGICAL DISEASES.
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CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

24. REGULATION OF GENE EXPRESSION IN NORMAL AND NEOPLASTIC CELLS. A REVIEW.
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25. WHAT ARE ISOZYMES TELLING US ABOUT GENE REGULATION IN CANCER?
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TRANSFORMATION GENE STRUCTURE

1. HUMAN EJ BLADDER CARCINOMA ONCOGENE IS HOMOLOGUE OF HARVEY SARCOMA VIRUS RAS GENE.

Parada LF, Tabin CJ, Shih C, Weinberg RA
Center for Cancer Res., Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA, 02139

Nature; 297(5866):474-478 1982

Examination of homologies between retroviral oncogenes and transforming sequences defined by transfection reveals that the human bladder carcinoma (EJ) oncogene is homologous to the Harvey sarcoma virus oncogene (ras). Structural analysis limits the region of homology to a 3.0-kilobase SacI fragment of the EJ oncogene. Both EJ and ras DNA probes detect similar transcripts in transfectants derived from bladder carcinoma cell lines. (Author abstract) (42 Refs)

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2. TRANSFORMING GENES OF HUMAN BLADDER AND LUNG CARCINOMA CELL LINES ARE HOMOLOGOUS TO THE RAS GENES OF HARVEY AND KIRSTEN SARCOMA VIRUSES.

Der CJ, Krontiris TG, Cooper GM
Sidney Farber Cancer Inst., Boston, MA, 02115
Proc Natl Acad Sci USA; 79(11):3637-3640 1982

Blot hybridization analysis indicated that NIH 3T3 mouse cells transformed by high mol wt DNAs of a human bladder and a human lung carcinoma cell line contained new sequences homologous, respectively, to the transforming genes of Harvey (rasH) and Kirsten (rasK) sarcoma viruses. The unique ras sequences were present in multiple independent NIH cell lines transformed in both primary and secondary transfection assays and corresponded to ras sequences normally present in human DNAs. The ras gene product was expressed in NIH cells transformed by bladder carcinoma DNAs and in the human bladder carcinoma cell lines at levels two- to four-fold greater than the level observed in nontransformed NIH 3T3 cells. These results indicate that the transforming genes of these human tumor cell lines are the cellular homologs of two retroviral transforming genes. (Author abstract) (30 Refs)

3. ISOLATION OF A TRANSFORMING SEQUENCE FROM A HUMAN BLADDER CARCINOMA CELL LINE.

Shih C, Weinberg RA
Dept. Molecular Biology, Massachusetts General Hosp., Bostin, MA, 02139
Cell; 29(1):161-169 1982

We have isolated the component of human bladder carcinoma cell DNA that is able to transform mouse fibroblasts. The oncogenic sequence was isolated initially from a lambda phage genomic library made from DNA of a transfected mouse cell carrying the human oncogene. A subcloned insert of 6.6 kb that carried transforming activity was amplified in the plasmid vector pBR322. The subcloned oncogene has been used as a sequence probe in Southern blot analyses. The oncogene appears to derive from sequences present in normal cellular DNA. Structural analysis has failed so far to reveal differences between the oncogene and its normal cellular homolog. The oncogene is unrelated to transforming sequences detected in a variety of other types of human tumor cell lines derived from colonic and lung carcinoma and from neuroblastoma. In contrast, the EJ bladder oncogene appears closely related to one that is active in the human T24 bladder carcinoma cell line. The oncogene appears to have undergone little, if any, amplification in several bladder carcinoma cell lines. (Author abstract) (35 Refs)

4. ONCOGENES OF SPONTANEOUS AND CHEMICALLY INDUCED TUMORS.

Weinberg RA
Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
Adv Cancer Res; 36:149-163 1982

The value of experiments involving the process of gene transfer, termed transfection, in resolving questions concerning the role of DNA damage in oncogenic transformation is discussed. Topics reviewed include a model of cellular oncogenes; the retrovirus-associated oncogenes; oncogenes of cells transformed by chemical carcinogens; the transforming genes in 3-methylcholanthrene-transformed cells; types of transformed cells yielding focus-induced DNA; the multiplicity of human oncogenes; and analogies between virus-and non-virus-induced cellular oncogenes. The process of activation of oncogenes, the role of oncogenes in carcinogenesis and maintenance of phenotype, and the proteins encoded by activated oncogenes are discussed. It is unlikely that activation of a cellular oncogene is the only necessary alteration occurring during the conversion of a normal cell into a tumor cell; other genetic and epigenetic controls are probably involved in realization of the oncogenic phenotype. Experiments to date suggest, however, that a multistep process is not involved, and that a single genetic determinant is able to effect the conversion of the recipient cell from normal fibroblast into highly tumorigenic fibrosarcoma cell. It is possible that recipient cells in such experiments already have undergone many necessary predisposing steps, and that only the final alteration is provided by the transfected oncogene. (34 Refs)

5. MALIGNANT TRANSFORMATION OF HUMAN EMBRYO RETINOBLASTS BY CLONED ADENOVIRUS 12 DNA.

Byrd P, Brown KW, Gallimore PH
Cancer Res. Campaign Laboratories, Dept. Cancer Studies, Medical Sch., Univ. Birmingham, Birmingham B15 2TJ, England
Nature; 298(5869):69-71 1982

Isolation of a recombinant plasmid (pAsc2)-trans human embryo retinoblast (HER) cell line that contains many copies of the adenovirus Type 12 (Ad 12) transforming region, expresses virus-specified proteins, and following inoculation into athymic mice, forms tumors which resemble retinoblastomas is described. Primary cultures of human retinoblasts were transfected with pAsc2, and one transformed focus, identified 45 days after transfection, was isolated and established as a continuous cell line. The cell line has been designated Ad 12 HER1 and was the first reported Ad 12-transformed human cell line. Cytogenetic analysis revealed a pseudotetraploid human karyotype. The Ad 12 HER1 cell line was grown beyond the thirty-sixth tissue culture passage level and at no time has its growth entered a crisis phase. When Ad 12 HER1 cell DNA was digested with the restriction endonucleases BglII or SstI and subjected to Southern blotting analysis using P-labeled Ad 12 EcoRI-C DNA fragments as a probe, Ad 12 sequences were found on many DNA fragments whose sizes ranged from greater than 12 kilobase pairs (kb) to 2.2 kb. As these enzymes cleave host DNA sequences only, each fragment represented a separate insert of pAsc2 sequences. Results suggested that Ad 12 HER1 cells contain intact, integrated copies of viral and vector sequences and it is likely that some of the inserts contain tandem repeats of the entire recombinant plasmid. Histological analysis of the Ad 12 HER1-induced tumors showed them to consist of clusters of small cells with many mitotic figures characteristic of poorly differentiated human retinoblastomas. (29 Refs)

6. TRANSFORMATION OF NIH 3T3 CELLS WITH CLONED FRAGMENTS OF HUMAN CYTOMEGALOVIRUS STRAIN AD169.

Nelson JA, Fleckenstein B, Galloway DA, McDougall JK
Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
J Virol; 43(1):83-91 1982

NIH 3T3 cells were transfected with restriction endonuclease and cloned human cytomegalovirus DNA fragments to identify the transforming region(s). Cleavage of human cytomegalovirus strain AD169 DNA with XbaI and HindIII left a transforming region intact whereas EcoRI inactivated this function. Transfection of cells with cosmids containing human cytomegalovirus DNA spanning the entire genome resulted in transformation by one cosmid, pCM1058, with the AD169 HindIII DNA fragments E, R, T, and a'. Cells were selected for their growth in 1.2% methylcellulose. The clones isolated had a significant replating efficiency and were oncogenic in BALB/c nu/nu mice. Transfection of cosmids and plasmids containing subsets of the viral sequences in pCM1058 identified a common region possessed by all of the transforming recombinant molecules. This region was in the HindIII E fragment with the left boundary defined by the EcoRI d-R junction and the right boundary defined by the HindIII E-T junction. Further mapping and transfection experiments determined that the transforming region was contained within a 2.9-kilobase fragment between map units 0.123 and 0.14 on the prototype molecule of the AD169 strain. (Author abstract) (56 Refs)

7. MAPPING OF RESTRICTION FRAGMENTS AND TRANSFORMING ABILITY OF ADENOVIRUS 31.

Sawada Y, Yamashita T, Kanda F, Sekikawa K, Fujinaga K
Dept. Molecular Biology, Cancer Res. Inst., Sapporo Medical Coll., Sapporo 060, Japan
Tumor Res (Sapporo); 16:7-17 1981

The cleavage maps of adenovirus 31 (Ad31) DNA with five restriction endonucleases and the localization of the transforming ability of the genome is reported. Specific fragments induced by restriction with EcoR1, BamH1, HindIII, SalI, and SmaI were identified via agarose gel electrophoresis. The fragments A and F of EcoR1 digests, the fragments B and E of BamH1 digests and the fragments C and G of HindIII digests were localized at the ends of the Ad31 genome. When the HindIII-C and G fragments were used to transfect subconfluent monolayers of 3Y1 cells, transformed foci became visible 3 wk later in the -G fragment-treated cultures. No transformation occurred in mock-transfected or -C fragment transfected cells. Thus the transforming ability of Ad31 is localized at the end of the genome where HindIII-G maps. (23 Refs)

8. MOLECULAR CLONING AND SEQUENCE DETERMINATION OF A MURINE SARCOMA VIRUS GENOME (MEETING ABSTRACT).

Van Beveren C, Van Straaten F, Papkoff J, Lai MH, Muller R, Hunter T, Verma IM
The Salk Institute, P. O. Box 85800, San Diego, CA, 92138
In Vitro; 18(3,part2):314 1982

Moloney murine sarcoma virus (Mo-MSV), isolated from a Moloney murine leukemia virus (Mo-MLV)-induced mouse rhabdomyosarcoma, is a helper-dependent, C-type retrovirus which elicits the rapid appearance of sarcomas at the site of injection in mice. The analysis of its genome indicated that the 5' half was essentially the same as that of helper Mo-MLV, whereas the 3' end contained a major substitution of cellular DNA. The amount of viral transforming product(s) obtained in infection was so low as to preclude detection by standard means, and no tumor-specific antiserum was produced in tumor-bearing animals. Upon molecular cloning of infectious, unintegrated Mo-MSV double-stranded DNA genomes, the determination of the nucleotide sequence of the 5833-nucleotide genome was greatly facilitated. It was then possible to predict the amino acid sequence of the product of the transforming v-mosMo gene. Peptides corresponding to the N- and C- termini of the putative protein were synthesized and used to raise antibodies in rabbits. Immunoprecipitation with sera against the 12-amino acid C-terminus permitted the identification of a 37kd product of the v-mosMo gene in acutely infected NIH-3T3 cells. The product exists in two forms which differ in degree of phosphorylation. No protein kinase activity has been demonstrated to be associated with either form. (no Refs)

9. SEQUENCE ORGANIZATION OF A VIRAL DNA INSERTION PRESENT IN THE ADENOVIRUS-TYPE-5-TRANSFORMED HAMSTER LINE BKH268-C31.

Westin G, Visser L, Zabielski J, Van Mansfeld AD, Petterson U, Rozijn TH

Dept. Microbiology, Biomedical Centre, Box 581, S-751 23 Uppsala, Sweden

Gene; 17(3):263-270 1982

The smaller viral insert present in the 268-C31 cell line was cloned using the lambda phage Charon 4A as a vector and the nucleotide sequence of the host-viral junctions. The organization of the flanking eukaryotic sequences was studied. Twenty clones out of 100,000 scored positive in the hybridization tests using intact Ad5 DNA as a probe. Results indicated the presence of many more viral insertions in the BHK268-C31 DNA than the two that could be detected by the conventional reassociation kinetic studies and blotting experiments. (26 Refs)

10. NUCLEOTIDE SEQUENCE OF THE TRANSFORMING GENE OF AVIAN MYELOBLASTOSIS VIRUS.

Rushlow KE, Lautenberger JA, Papas TS, Baluda MA, Perbal B, Chirikjian JG, Reddy EP

(c/o Papas) Lab. Molecular Oncology, NCI, Bethesda, MD, 20205

Science; 216(4553):1421-1423 1982

Avian myeloblastosis virus is defective in reproductive capacity, requiring a helper virus to provide the viral proteins essential for synthesis of new infectious virus. This virus arose by recombination of the nondefective helper virus and host cellular sequences present within the normal avian genome. These latter sequences are essential for leukemogenic activity. The complete nucleotide sequence of this region is reported. Within the acquired cellular sequences there is an open reading frame of 795 nucleotides starting with the initiation codon ATG (adenine, thymine, guanine) and terminating with the triplet TAG. This open reading frame could code for the putative transforming protein of 265 amino acids with a mol wt of approx 30,000. (Author abstract) (17 Refs)

11. THE COMPLETE NUCLEOTIDE SEQUENCE OF POLYOMA VIRUS AND IDENTIFICATION OF THE TRANSFORMING (CARCINOGENIC) GENES.

Soeda E

Natl. Inst. Genetics, Mishima, Shizuoka Prefecture 411, Japan

Nippon Nogeikagaku Kaishi; 56(1):31-37 1982

The polyoma virus is a small-type tumorigenic virus composed of a circular double strand DNA of 5,292 bases. The complete nucleotide sequence of the polyoma virus is described, and the mechanism of carcinogenesis of cells by the virus is clarified. Genetic analysis of the mutated region of wild and non-transformed strains of N18 is performed, and differences between the patterns of carcinogenesis of other papovaviruses (SV40, BKV, etc) and that of the polyoma virus are discussed. (39 Refs) (In JPN)

12. ACUTE LEUKEMIA VIRUSES E26 AND AVIAN MYELOBLASTOSIS VIRUS HAVE RELATED TRANSFORMATION-SPECIFIC RNA SEQUENCES BUT DIFFERENT GENETIC STRUCTURES, GENE PRODUCTS, AND ONCOGENIC PROPERTIES.

Bister K, Nunn M, Moscovici C, Perbal B, Baluda MA, Duesberg PH
Max-Planck-Institut fur Molekulare Genetik, Ihnestrasse 63-73, D-1000 Berlin 33, W. Germany
Proc Natl Acad Sci USA; 79(12):3677-3681 1982

The genetic structure and gene products of E26 virus were analyzed for a comparison with those of AMV. An E26/helper virus complex was found to contain two RNA species: a 5.7-kilobase (kb) RNA than hybridizes with cloned AMV-specific proviral DNA and hence is probably the E26 genome; and an 8.5-kb RNA that is unrelated to AMV and represents helper virus RNA. Thus, E26 RNA is smaller than 7.5-kb AMV RNA. Hybridization of size-selected poly(A)-terminating E26 RNA fragments with AMV-specific DNA indicated that the shared specific sequences are located in the 5' half of the E26 genome as opposed to a 3' location in AMV RNA. In nonproducer cells transformed in vitro by E26, a gag-related nonstructural 135,000-dalton protein (p135) was found. No gag (Pr76) or gag-pol (Pr180) precursors of essential virion proteins, which are present in AMV nonproducer cells, were observed. p135 was also found in cultured E26 virus producing cells of several leukemic chickens, and its intracellular concentration relative to that of the essential virion proteins encoded by the helper virus correlates with the ratio of E26 to helper RNA in virions released by these cells. p135 is phosphorylated but not glycosylated and appears to be coded for by a partial gag gene and by E26-specific RNA sequences, presumably including those shared with AMV. Hence, AMV and E26 appear to use different strategies for the expression of related onc sequences: AMV is thought to encode a transforming protein via a subgenomic mRNA, wherease E26 codes for a gag-related polyprotein via genomic RNA. It is speculated that differences in the oncogenic properties of E26 and AMV are due to differences in their genetic structures and gene products. (32 Refs)

TRANSFORMATION GENE EXPRESSION AND REGULATION

13. TRANSCRIPTS FROM THE CELLULAR HOMOLOGS OF RETROVIRAL ONCOGENES: DISTRIBUTION AMONG CHICKEN TISSUES.

Gonda TJ, Sheiness DK, Bishop JM
Dept. Microbiology and Immunology, Univ. California, San Francisco, CA, 94143
Mol Cell Biol; 2(6):617-624 1982

RNA transcribed from each the four c-onc genes c-myb, c-myc, c-erb, and c-src was quantified in a variety of tissues and cells by dot-blot assay with standardized avian myeloblastosis virus (AMV) 70S virion RNA. Cells examined for levels of c-onc RNAs included fibroblasts, whole embryo, yolk sac, Marek's disease-transformed cells (MSB-1), avian erythroblastosis virus (AEV) erythroblasts and fibroblasts and AMV myeloblasts. Transcription from each c-onc gene was detected (as c-myc, c-erb, and c-src RNA) in nearly all cells and tissues examined, but significant c-myb transcription was detected only in hemopoietic cells. The amount of c-onc RNAs varied, relatively little variation was observed in c-erb levels, a greater range in c-myc and c-src RNA levels was noted, and the greatest variations were exhibited by c-myb levels. Organs expressing the highest levels of c-myb (bone marrow, yolk sac, thymus) are major hemopoietic organs of the chicken, suggesting that c-myb may be expressed in immature hemopoietic cells. The high level of c-myb expression found in AEV-transformed erythroblasts suggests that c-myb function is not restricted to myelomonocytic cells. No obvious correlation existed between susceptibility to transformation and c-onc expression. (40 Refs)

14. HERPESVIRUS-SPECIFIC RNA AND PROTEIN IN CARCINOMA OF THE UTERINE CERVIX.

McDougall JK, Crum CP, Fenoglio CM, Goldstein LC, Galloway DA
Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Proc Natl Acad Sci USA; 79(12):3853-3857 1982

Cloned probes of herpes simplex virus type 2 DNA were used in cytological hybridization experiments to detect herpesvirus RNA transcripts in the neoplastic cells of tumors of the uterine cervix. Virus-specific RNA was shown to represent transcription of limited regions of the genome, of which one is known to code for a DNA-binding protein that can be found by immunoperoxidase staining in the neoplastic cells of these tumors and has also been detected in cells transformed in vitro by this virus. (Author abstract) (56 Refs)

15. VIRUS-SPECIFIC PROTEINS IN ADENOVIRUS TYPE 12-TRANSFORMED AND TUMOUR CELLS AS DETECTED BY IMMUNOPRECIPITATION.

Achten S, Doerfler W
Inst. Genetics, Univ. Cologne, 5 Cologne 41, Weyertal 121, W. Germany
J Gen Virol; 59(part2):357-366 1982

Adenovirus Type 12 (Ad12)-specific proteins were determined in nine well-characterized AD12-transformed hamster cell lines and in Ad12-induced hamster and rat tumor lines by immunoprecipitation, gel electrophoresis and autoradiography. All cell lines expressed a 60K mol wt polypeptide. In several cell lines, the presence of a 58K mol wt protein could also be demonstrated by these techniques. Smaller Ad12-specific proteins could be detected only in the Ad12-transformed hamster cell lines HA12/7 and A2497-3, and in the Ad12-induced hamster tumor line CLAC3. The quality of the immunoprecipitation tests performed depended primarily on the sera used; their antibody titers varied widely. For at least one of the Ad12-transformed hamster cell lines (HA12/7), there was good agreement in the number and mol wt of Ad12-specific proteins detected by both immunoprecipitation and in vitro translation of hybrid-selected cytoplasmic RNA. There was no clear-cut correlation between the number and the nature of Ad12-specific proteins and the way in which the cell lines or tumors were obtained. Cell lines with the least number of copies of Ad12 DNA persisting appeared to express the largest number of Ad12-specific proteins. (Author abstract) (34 Refs)

16. TUMORIGENIC TRANSFORMATION OF MAMMALIAN CELLS INDUCED BY A NORMAL HUMAN GENE HOMOLOGOUS TO THE ONCOGENE OF HARVEY MURINE SARCOMA VIRUS.

Chang EH, Furth ME, Scolnick EM, Lowy DR
Dept. Pathology, Uniformed Services Univ. of Health Sciences, Bethesda, MD, 20014
Nature; 297(5866):479-483 1982

A normal human gene homologous to the p21 ras oncogene of Harvey murine sarcoma virus induced oncogenic transformation and high p21 ras levels in murine fibroblasts when this gene was ligated to a control element (the long terminal repeat) from a murine or feline retrovirus. These results indicate that high levels of a gene product encoded by a normal human oncogene can induce tumorigenic transformation. (Author abstract) (37 Refs)

17. A TEMPERATURE-SENSITIVE DEFECT IN THE EXPRESSION OF A SARCOMA VIRUS TRANSFORMING GENE.

Horn P, Janice J
The University of Texas Health Science Center at Houston Graduate School, of Biomedical Science Houston, TX
Diss Abstr Int [B]; 42(11):4397-B 1982

The viral proteins synthesized by a Moloney murine sarcoma virus (Mo-MuSV) with a temperature-sensitive mutation in a function required for the maintenance of the transformed state (ts110) were examined. Normal rat kidney cells (NRK) were infected with the ts110 virus and a non-virus-producing cell clone, termed 6m2, was isolated. This cell clone had a malignant phenotype at 33 degrees, the permissive temperature, but changed to a normal phenotype at 39 degrees. Two viral proteins were detected in 6m2 cells. A 58,000 dalton protein (P58) was detected at both 33 degrees and 39 degree and contained only core protein (gag) coded sequences. An 85,000 dalton protein (P85) was detected only at 33 degrees and contained sequences of viral core proteins p15, pp12, and part of p30 as well as protein sequences attributed by peptide mapping to P23 and P38, two candidate viral mouse src (v-mos) gene products. These results provide good evidence that P85 is a gag-mos polyprotein. As expected for a functional mos-gene product, P85 synthesis preceded parameters characteristic of the transformed state, including changes in cell morphology, in the cytoplasmic microtubule complex (CMTC) and in the rate of hexose uptake. (no Refs)

18. LOSS OF VIRAL GENE EXPRESSION AND RETENTION OF TUMORIGENICITY BY ABELSON LYMPHOMA CELLS. .

Grunwald DJ, Dale B, Dudley J, Lamph W, Sugden B, Ozanne B, Risser R
McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706
J Virol; 43(1):92-103 1982

Lymphomas induced by the Abelson murine leukemia virus (A-MuLV) were examined for the expression of biochemical and biological markers associated with A-MuLV transformation before and after in vivo growth in genetically distinguishable host mice. Although all tumors and clonal lines derived from them initially expressed the A-MuLV-encoded gag fusion protein p160, they ceased synthesis of this molecule after several weeks of growth in vivo as ascites tumors. Transplanted clonal lines continued to express the alloantigenic marker H-2b and the isoenzyme marker Gpi-1b of the donor tumor cells, indicating that the cells were of donor and not host origin. Examination of cellular DNA obtained from p160-positive and derivative p160-negative lines indicated that p160-negative clones had lost A-MuLV-specific proviral sequences as detected by hybridization with several probes. Although the clonal lines no longer expressed p160, they retained their malignant phenotype and continued to express the Abelson antigen, a cell surface marker associated with A-MuLV lymphomagenesis. Continued expression of the A-MuLV genome was not required for maintenance of oncogenic potential under these conditions of in vivo tumor growth. (Author abstract) (38 Refs)

EXPERIMENTAL MODULATION OF ONCOGENIC TRANSFORMATION

19. EFFECTS OF TELEOCIDIN AND THE PHORBOL ESTER TUMOR PROMOTERS ON CELL TRANSFORMATION, DIFFERENTIATION, AND PHOSPHOLIPID METABOLISM.

Fisher PB, Miranda AF, Mufson RA, Weinstein LS, Fujiki H, Sugimura T, Weinstein IB
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Cancer Res; 42(7):2829-2835 1982

The potent tumor-promoting agent 12-O-tetradecanoylphorbol-13-acetate (TPA) and related diterpene phorbol esters have been shown to enhance viral transformation and anchorage-independent growth, inhibit differentiation, and stimulate phosphatidylcholine turnover in various cell culture systems. In the present study, we report that teleocidin, an indole alkaloid isolated from Streptomyces, induces several biological effects similar to those of TPA in cell culture. Both TPA and teleocidin enhanced transformation of a clone of Fischer rat embryo cells (CREF) by a temperature-sensitive mutant of adenovirus Type 5 (H5ts125); enhanced the cloning efficiency in agar of E11 cells, a clone of H5ts125-transformed Sprague-Dawley rat embryo cells; inhibited melanogenesis in murine B-16 melanoma cells; inhibited myogenesis in myoblast cultures established from normal human skeletal muscle; and stimulated choline release from prelabeled phospholipids of C3H10T1/2 mouse cells. In general, TPA and teleocidin were equipotent in inducing these biological effects and were most active in the 3-to 10-ng/ml range, ie, approximately 10(-8) to 10(-9) M. These studies provide further evidence that teleocidin represents a new class of tumor-promoting agents with properties similar to, if not identical with, those of the phorbol ester tumor promoters. These findings also suggest that cell culture systems can be used to identify new types of tumor-promoting agents in addition to the diterpene phorbol esters. (Author abstract) (58 Refs)

20. RESTING STATE DEPTH AND SATURATION DENSITY AS MODULATED BY TUMOR PROMOTERS AND CULTURE CONDITIONS: RELATIONSHIP TO CHEMICAL TRANSFORMATION IN C3H/10T1/2 CELLS.

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JNCI; 68(2):259-266 1982

With the use of cultures of C3H/10T1/2 fibroblasts, the relationships of saturation density and cell resting state (G0) depth to oncogenic transformation by 3-methylcholanthrene (MCA) were investigated. The tumor promoter 12-O-tetradecanoylphorbol 13-acetate (TPA), caused a small increase in the saturation density, but saccharin (SAC), a suspected promoter, did not Correspondingly, TPA tested positively as a promoter of transformation in a typical two-stage transformation assay with these cells while SAC did not. By altering the confluent-phase serum concentration and/or the medium renewal frequency of MCA-treated cultures, it was found that the magnitude of transformation for a given concentration of MCA was independent of the saturation density. Oscillations in this density were observed even when the medium was renewed as frequently as every 3 days, indicating that cell death and replacement occur during what is generally regarded to be a period of cellular stability. Neither TPA nor SAC blocked the cells from progressing into deeper resting states over time, as indicated by the prereplicative lag time after a medium change at 42 days. However, the serum concentration and medium renewal frequency did affect the resting state depth. Daily renewals with medium containing 10% serum blocked the resting state from deepening and kept the cells from achieving a saturation density. Under these circumstances, transformation was completely inhibited in MCA-treated cultures. (Author abstract) (38 Refs)

21. DISSOCIATED OCCURRENCE OF SINGLE-GENE MUTATION AND ONCOGENIC TRANSFORMATION IN C3H 10T1/2 CELLS EXPOSED TO ULTRAVIOLET LIGHT AND CAFFEINE.

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J Cell Physiol; 111(3):309-314 1982

Effects of caffeine and UV light on postreplication repair were studied in C3H mouse embryo-derived 10T1/2 cell clones between passages 11-15. Alkaline sucrose gradient sedimentation experiments showed that the DNA synthesized by 10T1/2 cells after UV irradiation was of reduced mol wt when compared to parental DNA. When cells were exposed to 1 milliM caffeine after UV irradiation the DNA repair was severely inhibited. Results indicated that caffeine potentiated the killing of 10T1/2 cells by UV light. Caffeine was effective in enhancing cell killing at all UV doses tested although the differential effects between 0.5 and 1 milliM were less pronounced at higher UV doses. With UV doses of 5 and 10 Joule/square meter (J/m2), the addition of caffeine resulted in higher transformation frequencies. The rate of increase at two UV doses were 2.4- and 2.3-fold/milliM caffeine, respectively. When the transformation of unirradiated cells exposed to caffeine for 48 hr was measured, caffeine alone induced transformation. However, the transformation potentiation effect of 1 milliM caffeine after 10 J/m2 was statistically significant. The potentiation factor was 1.7. Caffeine by itself did not induce detectable ouabain-resistant mutations in 10T1/2 cells; a possible inhibitory effect was observed. Results indicate that gene mutation and malignant transformation in 10T1/2 cells can be dissociated. (45 Refs)

22. IS TRANSFORMATION ASSOCIATED WITH AN INCREASED ERROR FREQUENCY IN MAMMALIAN CELLS?

Pollard JW, Harley CB, Chamberlain JW, Goldstein S, Stanners CP
Dept. Biochemistry, Queen Elizabeth Coll., Univ. London, Campden Hill, London W8 7AH, England
J Biol Chem; 257(11):5977-5979 1982

Acute starvation of mammalian cells for amino acids results in translational errors that may be detected by two-dimensional polyacrylamide gel electrophoresis. Using this as an assay for error frequency in mammalian cells, we investigated the hypothesis that neoplastic transformation was associated with an increased error frequency which in turn leads to an increased mutation rate and a decreased efficiency of regulatory controls (phenomena of tumor progression). Although we found that transformation was not always associated with an increased level of mistranslation we showed that SV40 transformation increased the level of translational errors in all cell types tested. (Author abstract) (27 Refs)

23. FIBROBLAST GROWTH FACTOR STIMULATES ANCHORAGE INDEPENDENT GROWTH IN AGAR OF BHK21/13 AND SV3T3 CELLS.

Zumbe A, Burk RR
Nestle Res. Lab., 1814 La Tour-de-Peilz, Switzerland
Cell Biol Int Rep; 6(5):503-511 1982

Growth of secondary baby hamster kidney fibroblasts, the partially transformed cell line BHK21/13, and the virally transformed derivatives SV3T3 and SV28 in soft agar was studied, and the response to fibroblast growth factor (FGF) was assessed. Only BHK21/13 cells responded to FGF in soft agar. Secondary hamster baby hamster kidney fibroblasts in suspension did not grow, even with FGF; SV28 cells grew independently of FGF. Balb/c 3T3 cells behaved like the secondary baby hamster kidney cells, and SV3T3 like BHK21/13, suggesting three degrees of transformation. (17 Refs)

24. HUMAN TERM PLACENTA CONTAINS TRANSFORMING GROWTH FACTORS.

Stromberg K, Pigott DA, Ranchalis JE, Twardzik DR
Lab. Viral Carcinogenesis, NCI, Frederick, MD, 21701
Biochem Biophys Res Commun; 106(2):354-361 1982

The isolation of three transforming growth factors (TGFs) of mol wt 6,000, 10,000 and 20,000 daltons from normal human placenta is reported. Each of these activities had characteristic properties of TGFs in that each stimulated anchorage-independent growth of normal rat fibroblasts and each competed with 125I-epidermal growth factor for receptor binding to epidermal growth factor (EGF) receptor rich human carcinoma cells. Each fraction scored in the radioreceptor assay in proportion to its normal rat kidney growth-promoting activity in soft agar. Although originally suspected to be EGF, the 6,000 mol wt fraction was shown to be a different polypeptide. Each of the four TGFs required intact disulfide bonds and withstood exposure to urea and repeated lyophilization. A several fold increase in activity was observed when the 6,000 mol wt fraction was treated with trypsin. Papain treatment, however, did strongly inhibit soft agar-stimulating activity. This system, utilizing readily available human placental tissues can be valuable in studying the progression from normalcy toward hydatidiform mole and choriocarcinoma, and the action of TGFs in stimulating this change. (19 Refs)

BIOCHEMICAL AND MOLECULAR BIOLOGICAL STUDIES OF TRANSFORMED PHENOTYPE

25. MONOCLONAL ANTIBODIES TO THE P21 PRODUCTS OF THE TRANSFORMING GENE OF HARVEY MURINE SARCOMA VIRUS AND OF THE CELLULAR RAS GENE FAMILY.

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J Virol; 43(1):294-304 1982

We have isolated eight rat lymphocyte-myeloma hybrid cell lines producing monoclonal antibodies that react with the 21,000-dalton transforming protein (p21) encoded by the v-ras gene of Harvey murine sarcoma virus (Ha-MuSV). These antibodies specifically immunoprecipitate both phosphorylated and non-phosphorylated forms of p21 from lysates of cells transformed by Ha-MuSV. All eight react with the products of closely related ras genes expressed in cells transformed by two additional sarcoma viruses (rat sarcoma virus and BALB sarcoma virus) or by a cellular Harvey-ras gene placed under the control of a viral promoter. Three of the antibodies also react strongly with the p21 encoded by the v-ras gene of Kirsten MuSV. These same three antibodies immunoprecipitate the predominant p21 species synthesized normally in a variety of rodent cell lines, including the p21 produced at high levels in 416B murine hemopoietic cells. This suggests that an endogenous gene closely related to Kirsten-ras is expressed in these cells. The monoclonal antibodies have been used to confirm two properties associated with p21: localization at the inner surface of the membrane of Ha-MuSV-transformed cells, assayed by immunofluorescence microscopy, and binding of guanine nucleotides. (Author abstract) (42 Refs)

26. PP60SRC-DEPENDENT INCREASE IN ADENOSINE-STIMULATED CAMP FORMATION.

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Exp Cell Res; 139(2):436-439 1982

Responsiveness to extracellular signals may participate in the control of cell division. This hypothesis was examined by comparing the adenosine responsiveness of Rous sarcoma virus (RSV)-transformed cells and untransformed cells. The results show that RSV-transformed chicken embryo cells (CEC) are more responsive to adenosine than Rous associated virus (RAV)-infected or normal CEC. Experiments using temperature-sensitive, transformation-defective (ts-td) RSV-CEC grown under permissive and restrictive temperatures exhibit the same differences as RSV- and RAV-infected cells, respectively. Moreover, the ts-td virus-infected cells exhibit an enhanced adenosine responsiveness within 1 hr following a shift from the restrictive to the permissive temperature. These data indicate that increased adenosine responsiveness is an early event in RSV-induced transformation of CEC. (Author abstract) (28 Refs)

27. IDENTIFICATION OF PHOSPHOTYROSINE-CONTAINING PROTEINS IN UNTRANSFORMED AND ROUS SARCOMA VIRUS-TRANSFORMED CHICKEN EMBRYO FIBROBLASTS.

Martinez R, Nakamura KD, Weber MJ
Dept. Microbiology, Univ. Illinois, Urbana, IL, 61801
Mol Cell Biol; 2(6):653-665 1982

A methodology for identification of proteins which are phosphorylated on tyrosine residues by their mol wt is described. 32P-labeled whole cell lysates were electrophoresed through tubular polyarcylamide gels, and the phosphoamino acid content of the separated phosphoproteins was analyzed. Analysis of Rous sarcoma virus (RSV)-transformed chick embryo fibroblast cell lysates revealed a large number of phosphotyrosine-containing proteins encompassing a very wide range of mol wt (less than 20-greater than 200 kilodaltons). Application of the technique to untransformed cells indicated that the cells contain at least two major tyrosine-phosphorylated proteins. The transforming protein of RSV (pp60src) seems to directly or indirectly trigger a complex network of tyrosine phosphorylation events involving a large number of cellular proteins. The methodology presented is sufficiently sensitive to detect phosphotyrosine-containing proteins in cells characterized by low levels of total phosphotyrosine, such as untransformed cells. The method may prove useful for detecting minor tyrosine phosphorylation events that could occur after neoplastic transformation by agents that do not raise the overall phosphotyrosine level, such as papovaviruses, other retroviruses, and chemical carcinogens. (35 Refs)

28. THE INCREASE IN HORMONE-STIMULATED ADENYLATE CYCLASE ACTIVITY FOLLOWING ROUS SARCOMA VIRUS TRANSFORMATION.

Howard RF, Friis RR, Sheppard JR, Glossmann H
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J Cell Physiol; 111(3):295-302 1982

Ability of prostaglandin E1 (PGE1) and isoproterenol (ISP) to elevate the intracellular concentration of cyclic AMP (cAMP) was studied in uninfected cells, cells infected and transformed by Rous sarcoma virus (RSV) and Rous associated virus (RAV). Uninfected chicken embryo cells (CEC), cells infected but not transformed by RAV, and RSV-transformed cells in culture immediately synthesized increased amounts of cAMP upon exposure to 10 uM ISP, 10 uM PGE1, or prostaglandin E2. RSV-transformed cells were consistently more responsive to maximal stimulatory concentrations of ISP than uninfected and RAV-infected cells. RSV-transformation was observed to alter the adenylate cyclase activity measured by CEC membrane preparations. The time courses for the hormone stimulation of intact RSV-transformed and RAV-infected cells suggested that the untransformed cells were rapidly desensitized during continued beta-adrenergic receptor stimulation, while the transformed cell cultures continued to respond to ISP. Results indicated that transformed cells possess a greater number of beta-adrenergic receptors, and are more slowly desensitized by stimulatory concentrations of ISP. Membranes prepared from transformed cells specifically bound greater than 5x the quantity of radiolabeled (-)3H-dihydroalprenolol and 125I-iodocyanopindolol as compared with the untransformed cell membranes suggesting that the major difference in the untransformed and transformed cells is in the concentration of membrane beta-adrenergic receptors and the inability of

RSV-transformed cells to self-limit their response to specific external stimuli. (43 Refs)

29. MECHANISM OF TRANSFORMATION BY ROUS SARCOMA VIRUS: EVENTS WITHIN ADHESION PLAQUES.

Rohrschneider L, Rosok M, Shriver K
Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
Cold Spring Harbor Symp Quant Biol; 46(part2):953-965 1981

Using several mutants of Rous sarcoma virus which contain partial lesions in the src gene, various molecular events within adhesion plaques of infected chicken embryo cells were examined in order to determine their contribution to the transformed phenotype. The disposition of pp60v-src, vinculin, fibronectin, and stress fibers and the phosphorylation of vinculin on tyrosine within chicken embryo cells infected with partial-transformation mutants are diagrammed. (32 Refs)

30. CARBOXY TERMINUS OF POLYOMA MIDDLE-SIZED TUMOR ANTIGEN IS REQUIRED FOR ATTACHMENT TO MEMBRANES, ASSOCIATED PROTEIN KINASE ACTIVITIES, AND CELL TRANSFORMATION.

Carmichael GG, Schaffhausen BS, Dorsky DI, Oliver DB, Benjamin TL
Dept. Microbiology, Univ. Connecticut, Sch. Medicine, Farmington, CT, 06032
Proc Natl Acad Sci USA; 79(11):3579-3583 1982

We have constructed a transformation-defective polyoma virus mutant (Py 1387-T) that directs the synthesis of a normal small tumor antigen, a functional large tumor antigen, and a truncated (51,000-dalton) middle-sized tumor (mT) antigen that lacks 37 amino acids at its COOH terminus. The shortened mT polypeptide is missing the hydrophobic 'tail' thought to be responsible for the anchorage of this protein into the plasma membrane and is in fact in cytosol fractions. This truncated mT polypeptide is inactive in an in vitro protein kinase assay and is altered in its phosphorylation in vivo. Mutant 1387-T differs from wild-type virus in having a T-A base pair instead of a C-G base pair at nucleotide position 1387. This change was introduced into viral DNA by using a synthetic undecanucleotide as a specific mutagen. Wild-type polyoma DNA was rendered single stranded by molecular cloning into coliphage M13. The oligonucleotide, which hybridizes with a mismatch at the site to be altered, was used to prime the synthesis of double-stranded closed circular DNA. Progeny recombinant phages were screened by DNA sequence analysis for the desired base change. The polyoma mutant was reconstructed from recombinant phage replicative form DNA molecules containing the mutation. (Author abstract) (45 Refs)

31. CHARACTERIZATION OF AN AMINO ACID FUCOSIDE OF NORMAL AND SV40-TRANSFORMED HUMAN EMBRYONIC LUNG CELLS.

Morton PA, Klinger MM, Steiner SM
(c/o Steiner) T. H. Morgan Sch. Biological Sciences, Univ. Kentucky, Lexington, KY, 40506
Cancer Res; 42(8):3022-3027 1982

The incorporation of radioisotopically labeled fucose into a prominent fucosylated component, ie, fucose-labeled amino acid fucoside 4c (FL4c), of human embryonic lung cells is markedly decreased in cell lines derived from human tumors. In the current study, we have extended the above observations by examining more closely related normal and transformed human cells, eg, W138 cells and SV40-transformed W138 cells. We have found that the level of radioisotopically labeled fucose incorporated into FL4c of the SV40-transformed human embryonic lung cells is dramatically reduced as compared to their normal counterpart cells. Additionally, we have chemically characterized FL4c. FL4c was purified from monkey tissues using a combination of gel filtration chromatography, ion-exchange chromatography, and preparative thin-layer chromatography. Analysis of this material was accomplished by amino acid analyzer and by gas-liquid chromatography; fucose, glucosamine, and aspartic acid in molar ratios of approximately 1.0:1.0:1.0 were observed. Furthermore, alpha-L-fucosidase treatment of [3H]fucose-labeled FL4c revealed that the fucose was alpha-linked and in a terminal position. Similar treatment of [3H]glucosamine-labeled FL4c yielded a component that cochromatographed with N-acetylglucosaminylasparagine. The combined results of the structural studies are consistent with the structure of FL4c being alpha-fucosyl-N-acetylglucosaminylasparagine. (Author abstract) (25 Refs)

32. ANTIGENIC CHANGES IN NONHISTONE PROTEINS DURING AZO DYE HEPATOCARCINOGENESIS.

Schmidt WN, Gronert BJ, Page DL, Briggs RC, Hnilica LS
Dept. Biochemistry, Vanderbilt Univ. Sch. Medicine, Nashville, TN, 37232
Cancer Res; 42(8):3164-3174 1982

We have investigated the appearance of specific nonhistone proteins during azo dye induced hepatocarcinogenesis in the rat. Groups of animals fed azo dye-containing diet were sacrificed at approx 3-wk intervals, portions of their livers were examined histologically, and the remaining material was fractionated into chromatin and cytoplasmic fractions. Livers of the azo dye-fed animals exhibited histological changes that have been classically attributed to the course and development of cancer; by 28 to 30 wk of treatment, nearly all animals had developed hepatomas. Heterogeneous rabbit antisera were prepared to dehistonized chromatin from several azo dye-induced hepatomas. These antisera were then used to assess various chromatins for the appearance of antigens specific for neoplasia during induced carcinogenesis using immunodetection of antigens separated electrophoretically and transferred to nitrocellulose. Changes in the immunoreactivity of liver chromosomal proteins during carcinogen treatment were evident after 3 wk, and the antigenic profiles of various chromatin samples gradually assumed the characteristics of the hepatoma. The transformation was accompanied by qualitative changes in chromosomal protein antigens, and although these antigenic species were not directly quantitated, noticeable enrichment of tumor-specific species occurred with treatment time. Immunotransfer assays of cytoplasmic fractions indicated most antigens to be specific for chromatin. Normal tissue chromatin exhibited minimal immunoreactivity, and slightly more antigenic homology was noted with regenerating liver and most transplantable tumor chromatins. Interestingly, the transplantable tumor Walker 256 carcinosarcoma was highly enriched in antigens recognized by antisera to azo dye hepatoma dehistonized chromatin. These studies establish a definite chronological correlation between the chemical induction of cancer and sequential changes in the immunological specificity of nonhistone protein antigens. (Author abstract) (56 Refs)

33. INDUCTION OF NEOPLASTIC CELL GROWTH BY QUIESCENT CELLS IS MEDIATED BY SERUM CONCENTRATION AND CAMP PHOSPHODIESTERASE INHIBITORS.

Bertram JS, Bertram BB, Janik P
Grace Cancer Drug Center, Roswell Park Memorial Inst., Buffalo, NY, 14263
J Cell Biochem; 18(4):315-538 1982

Studies have shown that for transformed mouse fibroblasts (C3H/101/2) and Lewis lung carcinoma model systems, the expression of transformation is conditional upon the permissive behavior of neighboring cells. Such permissive behavior could be due to a failure in intercellular communication or to a failure in signal reception or processing. For a constant plating density an increase in serum concentration was shown to cause a dose responsive decrease in N-methyl-N-nitro-N-nitrosoguanidine (MNNG)-induced transformation frequency in fibroblast cells. This increase in serum concentration produced an increase in saturation density of confluent cells. A model is developed which suggests that interference in communication between cells occurs during transformation. The passage of small growth inhibitory substances through gap junctions between contacting cells controls cell cycle phase. Autonomous growth would occur through attenuation of signal intensity. This studies have identified two possible factors which may control signal strength, ie, cell density and elevated cAMP. The model thus suggests that transformed cells are deficient in their ability to form communication channels with themselves or with adjacent normal cells. The major effect of phosphodiesterase inhibitors may be to increase the latent period between tumor injection and the appearance of tumor. Applications of the model to phosphodiesterase inhibitors and to tumor promotion are discussed. (42 Refs)

34. TRIGLYCERIDE AND CHOLESTEROL ESTER METABOLISM OF RAT 1 CELLS AND ROUS SARCOMA VIRUS-TRANSFORMED RAT 1 CELLS.

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Cold Spring Harbor Lab., Cold Spring Harbor, NY, 11724
Exp Cell Res; 139(2):396-400 1982

The incorporation of 14C-long-chain fatty acids into the neutral lipids of rat 1 cells and B77 Rous Sarcoma Virus-transformed rat 1 cells was compared. Increased labeling of the cholesterol ester and triglyceride fractions was observed in the transformed cells. In temperature shift experiments, using B77 ts src Rous Sarcoma Virus-transformed rat 1 cells, alterations of cholesterol esterification could first be detected 4-6 hr after shift to the permissive temperature. Changes in triglyceride metabolism could be shown as early as 4-6 hr after activation of the transforming gene function. It is concluded that alterations of neutral lipid metabolism are among the early effects of the transformation process. (Author abstract) (25 Refs)

35. CELL CYCLE VARIATION IN 125I-LABELED EPIDERMAL GROWTH FACTOR BINDING IN CHEMICALLY TRANSFORMED CELLS.

Robinson RA, Branum EL, Volkenant ME, Moses HL
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Cancer Res; 42(7):2633-2638 1982

The chemically transformed AKR-MCA and C3H/MCA-58 cell lines spontaneously arrest growth in the G1 phase of the cell cycle due to nutrient deficiency when grown to saturation density in medium with 10% fetal bovine serum. An examination of 125I-labeled epidermal growth factor (EGF) binding in rapidly growing and G1-arrested cells showed that the G1-arrested chemically transformed cells also have a 10-to 20-fold reduction in the amount of 125I-labeled EGF binding relative to the same cells in the rapidly growing state. Recovery of receptor activity by addition of serum-free medium was inhibited by actinomycin D and cycloheximide, suggesting that new messenger RNA synthesis as well as increased protein synthesis is necessary for the recovery of EGF binding. A comparison of EGF binding in C3H/MCA-58 cells and the transformed parent line in the rapidly growing state showed the same approx level of receptor activity. The rapidly growing AKR-MCA cells had approx one-tenth the amount of EGF binding as did the rapidly growing nontransformed parent line. Analysis of data showed a 10-fold greater number of receptors in the AKR-2B cells relative to the AKR-MCA cells with a lesser difference in receptor affinity. The chemically transformed BP-3T3, like the other two chemically transformed lines, was also demonstrated to arrest growth spontaneously due to nutrient deficiency with an associated 100-fold decrease in EGF binding. Rapidly growing BP-3T3 cells had only slightly less 125I-labeled EGF binding than did the nontransformed parent line in the rapidly growing state. The data indicate that one mechanism for reduction of EGF binding in chemically transformed cells is the propensity of these cells to arrest growth in G1 at saturation density due to low-mol-wt nutrient deficiency, a state associated with decreased EGF binding. (25 Refs)

36. PLASMINOGEN ACTIVATOR RELEASED AS INACTIVE PROENZYME FROM MURINE CELLS TRANSFORMED BY SARCOMA VIRUS.

Skriver L, Nielsen LS, Stephens R, Dano K
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Eur J Biochem; 124(2):409-414 1982

We have previously reported the purification of a plasminogen-activating serine protease with an approx Mr of 48,000 from sarcoma-virus-transformed murine cells. We now report that under serum-free conditions the enzyme is released from the cells in an inactive form. After affinity chromatography with 4-aminobenzamidine-cellulose, ion-exchange chromatography and gel filtration, the proenzyme could be obtained from culture fluid as a pure, homogeneous protein as evaluated by polyacrylamide gel electrophoresis with sodium dodecylsulfate. Proenzyme was quantitatively converted to active enzyme by incubation with catalytic amounts of plasmin. Analysis by polyacrylamide gel electrophoresis with sodium dodecylsulfate under reducing and nonreducing conditions showed that the inactive form consisted of a single polypeptide chain with an Mr of approx 48,000, while the active form consisted of two chains with Mr values of approx 18,000 and 29,000, held together by one or more disulfide bridges. The active-site reagent diisopropylfluorophosphate in radiolabeled form was incorporated into the 29,000-Mr chain of the active enzyme, but not into the inactive form. These findings provide conclusive evidence for the existence of an inactive proenzyme to this plasminogen activator and thus demonstrate an additional step in a cascade-like reaction leading to extracellular proteolysis. Regulatory as well as methodological implications of this finding are discussed. (Author abstract) (30 Refs)

37. PLASMINOGEN ACTIVATOR, FIBRONECTIN, LYMPHOTOXIN SENSITIVITY, AND NATURAL SKIN REACTIVITY RELATIONSHIPS TO GUINEA PIG CELL TUMORIGENICITY.

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Tumor Biology Section, Lab. Biology, Div. Cancer Cause and Prevention, NCI, NIH, Public Health Service, U.S. Dept. Health and Human Services, Bethesda, MD, 20205
JNCI; 68(2):329-336 1982

The quantitative expression of five properties of chemical carcinogen-induced, neoplastically transformed NIH strain 2 guinea pig fibroblasts was compared in cells possessing thousandfold differences in tumorigenicity. Plasminogen activator synthesis, sensitivity to lymphotoxin inhibition of cell proliferation, and the ability to induce a natural delayed tuberculin-type skin reaction in nonimmune syngeneic guinea pigs correlated directly with the number of cells required to produce a tumor. The most tumorigenic cells (10(2)-cell threshold dose) produced the most plasminogen activator, were most sensitive to lymphotoxin, and produced the greatest skin reactivity. Cells with a threshold tumor dose of 10(5)-10(7) cells exhibited the lowest expression of these properties. Fibronectin incorporation into an extracellular matrix was diminished in tumorigenic cells, as was anchorage-dependent growth; but neither diminished fibronectin incorporation nor the decreased anchorage requirement correlated quantitatively with the number of cells required to produce a tumor. The present investigation indicates that plasminogen activator synthesis, sensitivity to lymphotoxin, and the capacity of tumorigenic cells to induce natural delayed-type skin reactivity are among the factors that influence initial tumor growth. Plasminogen activator, an extracellular protease, may aid in the growth and spread of tumor cells in vivo by interfering with host fibrin deposition and by inactivating other host proteins such as lymphotoxin. (Author abstract) (46 Refs)

38. SELECTIVE PHAGOCYTOSIS OF CRYSTALLINE METAL SULFIDE PARTICLES AND DNA STRAND BREAKS AS A MECHANISM FOR THE INDUCTION OF CELLULAR TRANSFORMATION.

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Cancer Res; 42(7):2757-2763 1982

Crystalline NiS, CuS, CoS2, and CdS particles were actively phagocytosed by cells and potently induced morphological transformation of Syrian hamster embryo cells in a concentration-dependent fashion. In contrast, the respective amorphous metal sulfide particles (amorphous NiS, CuS, CoS, and CdS) were not as actively phagocytosed by cultured cells and, in comparison to the crystalline form of these compounds, induced considerably less morphological transformation at both cytotoxic and noncytotoxic exposure levels. Chemical reduction of positively charged amorphous NiS with LiAlH4 resulted in active phagocytosis of these particles which was also associated with enhancement of cellular transformation. Crystalline but not amorphous NiS caused considerable strand breaks in the DNA of Chinese hamster ovary cells following 2 to 3 hr exposure at 10 ug/ml as determined by alkaline sucrose gradient techniques with subsequent determination of DNA mol wt. Phagocytized inert particles such as latex beads did not induce transformation or DNA damage, suggesting that genotoxic dissolution products such as Ni2+ rather than the phagocytized particles are responsible for the observed DNA damage and cellular transformation. NiCl2 was about one-third to one-half as potent in inducing cellular transformation compared to crystalline NiS on a weight basis. These results correlate the selective phagocytosis of crystalline metal sulfides to their more potent activity in the induction of cellular transformation. (Author abstract) (18 Refs)

39. METABOLIC ACTIVATION OF BENZO(A)PYRENE BY TRANSFORMABLE AND NONTRANSFORMABLE C3H MOUSE FIBROBLASTS IN CULTURE.

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Cancer Res; 42(7):2697-2704 1982

Incubation of 2.5 uM benzo(a)pyrene (BaP) with C3H/10T1/2 or CVP3SC6 (CVP) mouse fibroblasts from 48 hr resulted in the metabolism of 36 to 42% of the BaP to organic soluble derivatives, which cochromatographed with 7,8-trans-dihydroxy-7,8-dihydrobenzo(a)pyrene, 9,10-trans-dihydroxy-9,10-dihydrobenzo(a)-pyrene, 3-hydroxybenzo(a)pyrene, and 9-hydroxybenzo(a)pyrene, or to water-soluble derivatives. The formation of both organic and water-soluble metabolites during the 48-hr period increased proportionally with time, except in the case of BaP phenols, which increased initially but then remained the same or decreased. The distribution of organic soluble metabolites in the extracellular culture medium consisted primarily of BaP diols and was significantly different from that found inside the cells. The intracellular profile of organic soluble metabolites produced by both cell lines consisted predominantly of BaP phenolic derivatives and was qualitatively similar to the spectrum of metabolites produced by the incubation of BaP with C3H/10T1/2 or CVP cell microsomes. The nature of the BaP water-soluble derivatives produced by the C3H/10T1/2 and CVP cell lines was investigated by hydrolysis of culture medium with beta-glucuronidase and arylsulfatase. Although sulfation was not a major conjugation pathway for BaP in these cells, glucuronidation of BaP phenols was found to account for 30% of the total water-soluble derivatives. The similarity in the kinetics and qualitative nature of the metabolism of BaP by C3H/10T1/2 and CVP cells indicates that both cell lines are equally capable of biosynthesizing the proximal carcinogen, 7,8-trans-dihydroxy-7,8-dihydrobenzo(a)pyrene. Analysis of the water-soluble metabolites produced by these cells suggests further that the nonresponsiveness of the CVP cells to BaP-induced transformation cannot be accounted for on the basis of an increased detoxication of 7,8-trans-dihydroxy-7,8-dihydrobenzo(a)pyrene. (Author abstract) (34 Refs)

40. SIMILARITIES IN THE FORMATION AND REMOVAL OF COVALENT DNA ADDUCTS IN BENZO(A)PYRENE-TREATED BALB/3T3 VARIANT CELLS WITH DIFFERENT INDUCED TRANSFORMATION FREQUENCIES.

Lo KY, Kakunaga T
Cell Genetics Section, Lab. Molecular Carcinogenesis, NCI, Bethesda, MD, 20205
Cancer Res; 42(7):2644-2650 1982

Classes of cell variants isolated from BALB/3T3-A31 clone 1 showing high, intermediate, and low susceptibility to ultraviolet light-induced transformation also demonstrated a differential response to benzo(a)pyrene (BP)-induced transformation. On the other hand, these variants showed an identical susceptibility to the killing effect of these carcinogens. The extent of BP binding to DNA was found to be very similar in all three classes of variants under transforming conditions. BP:DNA adducts from the variant cells were analyzed by high-pressure liquid chromatography. The same adducts (N2- *10S-[7R,8S,9R-trihydroxy-7,8,9-10 tetrahydrobenzo(a)pyrene]yl* deoxyguanosine and a minute amount of the 7S enantiomer) were detected in the highly susceptible, the intermediately susceptible, and the resistant variant clones. Removal of the BP:DNA adduct occurred at an equally slow rate in all three classes of variant cells. These results indicate that the formation of stable covalent DNA adducts is not a sufficient condition for induction of transformation. Processes other than formation and removal of the stably bound BP:DNA covalent adducts are thus major factors controlling the susceptibility of BALB/3T3-A31 clone 1 variant cells to BP-induced transformation. (Author abstract) (46 Refs)

41. ANALYSIS OF TYPE 5 ADENOVIRUS TRANSFORMATION WITH A CLONED RAT EMBRYO CELL LINE (CREF).

Fisher PB, Babiss LE, Weinstein IB, Ginsberg HS
Dept. Microbiology, Div. Environmental Sciences, Cancer Center/Inst. Cancer Res., Columbia Univ., New York, NY, 10032
Proc Natl Acad Sci USA; 79(11):3527-3531 1982

A recently isolated cloned cell line of Fischer rat embryo fibroblasts (CREF) can be transformed at high frequency by adenovirus serotype 5 (Ad5). The CREF cells display a near diploid karyotype, do not crisscross at confluency, can be maintained at confluency for greater than 7wk at 36 C, and do not form macroscopic colonies when seeded in agar. Transformed cells are identified by their altered morphology and the presence of adenovirus DNA sequences in the transformants, which can be demonstrated by lysing cells directly on nitrocellulose filters and hybridizing with 32P-labeled Ad5 DNA (spot hybridization). The frequency of transformation at 36 C is approx 2 x 10(-4) with wild-type Ad5 and approx 2 x 10(-3) with the temperature-sensitive mutant H5ts125. Southern blot hybridization analysis indicates that five out of six wild-type Ad5-and six out of six H5ts125-transformed CREF clones isolated at 36 C Contain the complete integrated Ad5 genome. Preliminary characterization of four transformed clones (2 wild-type and 2 H5ts125) indicates that, even though transformation was done in CREF cells (a clonal cell line), they differ in their biological properties, such as saturation density and anchorage dependence. (Author abstract) (31 Refs)

42. PROPERTIES OF DIHYDROFOLATE REDUCTASE FROM HUMAN TUMOURS (MEETING ABSTRACT)

Blair JA, Pheasant AE, Saleh AM, Sahota A, Whitburn SB, Oates GD, Allan RN
Department of Chemistry, University of Aston in Birmingham, Birmingham B4 7ET, England
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

Dihydrofolate reductase (DHFR) plays an important role in cell proliferation. Its inhibition arrests the cell cycle at the G1-S transition. 10-Formylfolate and 10-formylfolatetetraglutamate are formed by oxidation of the tetrahydro forms found in mammalian cells. Bovine liver DHFR does not reduce 10-formylfolate and is inhibited by 10-formylfolate and 10-formylfolatetetraglutamate (K equals 2x10-8M and 1.3 x 10-8M respectively). Lactobacillus casei DHFR reduces 10-formylfolate slowly and is weakly inhibited by it. In normal man 10-formylfolate is not reduced and inhibits the reduction of folic acid by DHFR. DHFR from some human intestinal and breast tumors slowly reduces 10-formylfolate and is weakly inhibited by it. Thus DHFR from these tumors is similar to the L casei enzyme and different from the normal mammalian enzyme. 13C nmr studies suggest that the reduced binding of 10-formylfolate to the L casei DHFR is caused by lack of a nucleophilic group on the enzyme. It is suggested that an important event in some malignant transformations is the synthesis via a mutated gene of a DHFR which no longer fully responds to a normal cell proliferation control mechanism. (no Refs)

43. CHEMICAL AND MOLECULAR BIOLOGICAL ASPECTS ALKYLHYDRAZINE-INDUCED CARCINOGENESIS IN HUMAN CELLS IN VITRO. INTERIM REPORT, 1 SEP. 1980-31 AUG. 1981.

Witiak DT
Coll. Pharmacy, Ohio State Univ., Columbus, OH
Chemical and Molecular Biological Aspects Alkylhydrazine-induced Carcinogenesis in Human Cells In Vitro. Interim Report, 1 Sep. 1980 - 31 Aug. 1981. Available from National Technical Information Service, Springfield, VA, as N82-19833:, 20 pp., 1981.

Carbon-14 labeled 1,1-DMH and 1,2-DMH of high specific activity were prepared and utilized, along with 14C-labeled MMH, to study alkylation of DNA and proteins in low passage human neonatal foreskin derived fibroblasts. When human fibroblasts were treated under conditions which would be expected to lead to a negligible number of transformation events, ie cells labeled were in a non-growing environment and the dose of methylhydrazine (1.6 microgram/ml) was well below the ED50 value (62-100 microgram/ml), significant differences in DNA and protein methylation were observed. For both protein and DNA, 1,2-DMH produced a higher degree of methylation than 1,1-DMH, with MMH demonstrating the lowest level. The data suggests that in these cells there are significant differences in the metabolic and/or chemical transformation of the methylhydrazines in the proposed active metabolite, methyl diazonium ion. (Author abstract)

CELL SURFACE PHENOMENA OF TRANSFORMATION

44. POSSIBLE ROLE OF A RETROVIRUS IN THE EXPRESSION OF TUMOR-SPECIFIC ANTIGENS OF THE METH A SARCOMA.

DeLeo AB, Chang KS, Wivel NA, Appella E, Old LJ, Law LW
Sloan-Kettering Cancer Center, New York, NY
Int J Cancer; 29(6):687-693 1982

The serologically defined tumor-specific surface antigen (TSSA) of the chemically-induced BALB/c Meth A sarcoma, highly restricted to 1 of 20 sarcomas of BALB/c origin, has been detected on a Moloney murine sarcoma virus (MoMuSV)-transformed BALB/c3T3 cell line, designated 11A(v). The immunogenicity of the 11A(v) cell in tumor-rejection assays was specific for the Meth A sarcoma, supporting the evidence for a close relationship between the TSSA and the tumor-associated transplantation antigen (TATA) of this tumor. Infection of SC-1 cells with retroviruses present in cultured filtrates of IIA(v) cells resulted in Meth A antigen expression. The retroviruses associated with Meth A antigen expression have been tentatively identified as replication and/or transformation-defective XC-MuLV. The possible roles of MoMuSV and cellular genes of the BALB/c strain of mice in the expression of the Meth A antigen are discussed. (Author abstract) (43 Refs)

45. DETECTION OF TUMOR ANTIGENS BY SYNGENEIC ANTISERUM ON IN VITRO-TRANSFORMED TRACHEAL EPITHELIAL CELL LINE 2-10-1.

Braslawsky GR, Kennel SJ, Steele V, Nettesheim P
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Int J Cancer; 29(6):677-681 1982

Sera obtained from rats showing transplantation immunity to syngeneic, malignant epithelial cell line, 2-10-1, were used to identify antigens associated with transformation in vitro. The 2-10-1 cell line was derived from exposure of tracheal explants, in vitro, to the carcinogen N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). Tumorigenic passages of the cell line were shown to have common antigenic determinants, shared by independently transformed malignant tracheal epithelial cell lines, as well as antigenic determinants that appear to be limited to the immunizing cell line, 2-10-1. Care was taken to ensure that antibodies were not produced against viral antigens or non-specifically absorbed serum components. Early passages of the 2-10-1 cell line were not tumorigenic in athymic BALB/c (nu/nu) mice, but became malignant with serial passage in vitro. Antigenic specificities recognized by 2-10-1 immune sera were also present on early-passage 2-10-1 cells that had not as yet acquired the malignant phenotype. Such antigen expression must be an early event in neoplastic development. (Author abstract) (20 Refs)

46. DETECTION OF A COMMON ANTIGEN ON MURINE B CELLS AND LYT-2+ T CELLS BY A RAT MONOCLONAL ANTIBODY, 14D10.

Kung JT, Sharrow SO, Mage MG, Paul WE
Lab. Immunology, NIH, Natl. Inst. Allergy and Infectious Diseases, Building 10, Room 11N311, Bethesda, MD, 20205
J Immunol; 129(1):81-86 1982

This paper reports the production of a rat monoclonal antibody, 14D10, which recognizes a determinant shared between B cells and Lyt-2+ T cells. Three subpopulations of spleen cells were defined based on the density of bound 14D10. They have been designated 14D10-SP (strongly positive), 14D10-WP (weakly positive), and 14D10-N (negative). Dual parameter immunofluorescence studies showed that 90% of 14D10-SP cells are IgM+ cells and more than 92% IgM+ cells are 14D10-SP. Of 14D10-WP cells, approx 60% are Lyt-1+2+ T cells and less than 10% are Igm+ cells. However, most (greater than 90%) of Lyt-2+ T cells are reactive with 14D10. Staining of purified populations of Lyt-2+ and Lyt-2(-) T cells with fluoresceinated 14D10 also showed greater than 90% of Lyt2+ T cells to be 14D10+, and fewer than 10% of Lyt-2(-) T cells are 14D10+. Mouse thymus contained very few (approx = 5%) 14D10+ cells. Analysis of bone marrow cells shows almost all small cells to be 14D10+. Six Abelson virus-transformed cell lines all express the antigen recognized by 14D10. (Author abstract) (19 Refs)

47. SCANNING ELECTRON MICROSCOPY STUDIES OF INTERACTION OF PROTEINS AND POLYAMINO ACIDS WITH ERYTHROBLASTS TRANSFORMED BY FRIEND VIRUS.

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ERRB, NICHD, Building 10, Room 12N206, Bethesda, MD, 20205
Cell Biol Int Rep; 6(5):443-453 1982

The effects of proteinaceous compounds (ovalbumin, concanavalin A, polysarcosine, gelatin, poly-L-lysine, lysozyme) on cell surface characteristics and adhesive properties of cultured HFL/d-tc erythroblasts transformed by Friend virus were studied by scanning electron microscopy. Both surface topography of individual cells and the ability to aggregate were affected by incubation with the compounds. (23 Refs)

MORPHOLOGICAL AND OTHER BIOLOGICAL ASPECTS OF ONCOGENIC TRANSFORMATION

48. MORPHOLOGICAL, IMMUNOLOGICAL, AND BIOCHEMICAL ANALYSES OF CHICKEN SPLEEN CELLS TRANSFORMED IN VITRO BY RETICULOENDOTHELIOSIS VIRUS STRAIN.

Shibuya T, Chen I, Howatson A, Mak TW
Dept. Medical Biophysics, Ontario Cancer Inst., Univ. Toronto, Toronto, M4X 1K9, Canada
Cancer Res; 42(7):2722-2728 1982

Reticuloendotheliosis virus strain T (REV-T) is a highly oncogenic avian retrovirus which causes a rapid neoplastic disease of the lymphoreticular system. We derived six cell lines from chicken spleen cells infected with REV-T. These cells can produce both the REV-T and its associated reticuloendotheliosis helper virus, REV-A. Histochemical analyses of these cells indicate that, while they are not stained by benzidine, peroxidase, beta-glucuronidase or acid alpha-naphthyl acetate esterase, they contain a high proportion (95%) of cells positive for acid phosphatase. Light and electron microscopic studies of these cells also revealed morphologies of lymphoblasts or activated lymphocytes with irregular nuclei and dispersed chromatin. Immunochemical analyses indicate that essentially all (90 to 100%) of the cells contain the surface marker Ia, but no cytoplasmic immunoglobulin M and immunoglobulin G could be detected by immunofluorescence staining. Results also show that some of these cell lines contain a low level of terminal transferase, and a proportion of these cells can be stained by an antiserum directed against chicken bursa cells. These results are consistent with the conclusion that the cells transformed by the highly oncogenic REV-T are lymphoid in nature. In addition, at least some of these cell clones may contain features characteristic of activated B-lymphocytes. Analysis of these cell clones indicates that some cell lines contain an adherent and nonadherent population with some differences in morphologies. In addition, electron microscopic examination revealed that, while the nonadherent cells are actively producing Type C viruses, Type C viruses are either absent or very rare in the adherent cell populations. These results support the conclusion that some of these cell lines are heterogeneous and contain subpopulations of cells with differences in their ability to produce viruses. (38 Refs)

49. SIMIAN VIRUS 40 A GENE FUNCTION: FURTHER CHARACTERIZATION AND GROWTH OF TSA TRANSFORMED CHINESE HAMSTER CELLS.

Robinson CC, Lehman JM
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J Cell Physiol; 111(3):225-231 1982

Characterization of the tsA transformants and their growth pattern on normal cell monolayers were studied using two simian virus 40 (SV40) transformed Chinese hamster embryo cell lines, ChHA58, transformed by group A mutant ts58, and the WT virus transformed cell line, ChHWT. Characteristics used to evaluate transformation of these cells are summarized. tsA mutant transformed ChH embryo cells at 40.5 C were distributed in all phases of the cell cycle and had heavily labeled nuclei after a short 3H-thymidine label indicating that they continue DNA synthesis at the restrictive temperature for T antigen. tsA transformed cells were seeded onto monolayers of normal Chinese hamster cells. Colonies of tsA transformed cells appeared at 37 C but not at 40.5 C while no difference in colony forming ability of WT transformants was observed at these two temperatures. During these experiments no debris accumulated in the culture fluid at 40.5 C, unlike the large numbers of floating dead cells present when the tsA transformants were grown alone. Results suggested that the growing pattern of tsA mutant transformed cells at 40.5 C might be different under the two culture conditions. Viable cells were necessary to obtain growth arrest since this effect was not observed with glutaraldehyde fixed cells or conditioned medium. These experiments demonstrated that under proper substrate conditions, tsA Chinese hamster cells were arrested in DNA synthesis. (26 Refs)

50. CYTOSKELETAL TARGETS FOR VIRAL TRANSFORMING PROTEINS WITH TYROSINE PROTEIN KINASE ACTIVITY.

Sefton BM, Hunter T, Nigg EA, Singer SJ, Walter G
Tumor Virology Lab., Salk Inst., San Diego, CA, 92138
Cold Spring Harbor Symp Quant Biol; 46(part2):939-951 1981

The phosphoamino acid compositions of several cytoskeletal proteins from both normal and transformed cells were analyzed in order to see if any of the proteins could be substrates for pp60src, which is localized in the cytoplasm of transformed cells. Vinculin, one of the proteins studied, contains increased levels of phosphotyrosine in Rous sarcoma virus-transformed cells and therefore may be a primary substrate for pp60src. (80 Refs)

51. COMPARISON OF CELLULAR GROWTH CHARACTERISTICS OF TRANSFORMED C3H 10T-1/2 CELLS ISOLATED FROM 14 DAY COLONY AND 38 DAY FOCUS AFTER EXPOSURE TO BENZO(A)PYRENE AND 1,3 DL DIEPOXYBUTANE (MEETING ABSTRACT).

Nelson RL, Garry VF
University of Minnesota, Minneapolis, MN, 55455
In Vitro; 18(3,part2):299 1982

Utilization of the C3H 10T-1/2 clonal cell line for morphologic transformation by chemical carcinogens has been restricted by the necessity of prolonged cultivation (4-6 weeks) before morphologic transformants can be accurately identified. In this report, we will present evidence for the observation of morphologic transformation of C3H 10T-1/2 colonies in 14 to 16 days after 24 hour carcinogen exposure to dose increments of Benzo(a)pyrene and diepoxybutane. Morphologic scoring of transformants is similar to the criteria put forward by Reznikoff et al. Overall, colony transformation frequencies appear to be lower than focus transformation frequencies by a factor of 2 at the corresponding dose. Transformed colony and foci isolates were compared for the following growth parameters at 2, 5, and 10 passages: plating efficiency, soft agar growth, doubling time and saturation density. Serial subcultivation of transformants shows marked differences in soft agar growth and saturation density patterns. Characteristically, foci isolates show rapid adaptation to soft agar growth; whereas transformed colony isolates are slowly adapted. Similar differences in the saturation density patterns of the isolates were noted. (no Refs)

52. HYBRIDS FROM FUSION OF TUMOR CELLS WITH NORMAL AND SV40 TRANSFORMED HUMAN FIBROBLASTS HAVE A FINITE IN VITRO LIFESPAN (MEETING ABSTRACT).

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W. Alton Jones Cell Science Center, Inc., Old Barn Road, Lake Placid, NY, 12946
In Vitro; 18(3,part2):283 1982

Human diploid cells have finite division potential in vitro, while tumor derived and virally transformed human cells divide indefinitely. To investigate the processes leading to the acquistion of indefinite proliferation, we have studied the proliferative potential of hybrids from normal x tumor and tumor x SV40 transformed cell fusions. We have previously found that 30-50% of hybrids from normal x SV40 transformed cell fusions were capable of extensive division (greater than 10 PD). However, when normal fibroblasts were fused with various human tumor cell lines, only 3% or less of the hybrids were able to divide extensively. It is therefore possible that different processes lead to indefinite proliferation in the SV40 vs tumor derived cell lines. If this is the case, tumor x SV40 transformed cell fusions might yield hybrids with finite lifespan. Fusion of an SV40 transformed human fibroblast with various tumor cell lines yielded 20% or fewer hybrids capable of extensive proliferation. When the tumor line was derived from a carcinoma, glioma or osteosarcoma, these hybrids eventually stopped dividing. Fusion with a fibrosarcoma, however, yielded hybrids that achieved at least 100 PD. These results demonstrate the dominance of the finite lifespan phenotype in normal x immortal cell fusions and suggest that different indefinitely proliferating lines arise due to loss of different specific regulatory functions. (no Refs)

ASSAYS OF ONCOGENIC TRANSFORMATION

53. CARCINOGEN-MEDIATED AMPLIFICATION OF SPECIFIC DNA SEQUENCES.

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Dept. Virology, Weizmann Inst. Science, Rehovot, Israel
J Cell Biochem; 18(2):149-156 1982

The development of an experimental system model , which utilizes simian virus 40 (SV40)-transformed Chinese hamster embryo cells, coupled with a highly sensitive in situ hybridization procedure for the detection of a single cell in which viral DNA synthesis has been induced, is presented. When exposed to chemical carcinogens such as benzo(a)pyrene, N-methyl-N'-nitro-N-nitrosoguanidine, 7,12-dimethyl benz(a)anthracene (DMBA), ethyl methanesulfonate aflatoxin B1, and 3-methylcholanthrene or physical carcinogens (gamma or UV radiation), SV40 DNA synthesis was induced in treated cells. Noncarcinogenic compounds such as phenanthrene and dibenz(a,c)anthracene had no effect. While carcinogen-induced amplification of SV40 DNA sequences is controlled by the viral 'A' gene, no infectious virus or complete SV40 DNA molecules were found in treated cells. DMBA treatment induced a heterogenous collection of DNA molecules with SV40 sequences. Analysis of Hirt's supernatant using restriction enzyme analysis of the amplified DNA molecules indicated that not all sequences in the integrated SV40 inserts are present. Amplification of SV40 DNA sequences may reflect a more general gene amplification phenomenon mediated by chemical carcinogens. (19 Refs)

54. MEETING REPORT: WORKSHOP ON THE PRACTICAL APPLICATION OF THE MAMMALIAN SPOT TEST IN ROUTINE MUTAGENICITY TESTING OF DRUGS AND OTHER CHEMICALS.

Braun R, Russell LB, Schoneich J

Zentralinstitut fur Genetik und Kulturpflanzenforschung der AdW der DDR, 4325 Gatersleben, E. Germany

Mutat Res; 97(2):155-161 1982

The mammalian spot test, which was developed in relation to radiation mutagenesis, is reviewed with respect to treatment procedure, spot classification, statistical evaluation, and interpretation of results. Variables regarding treatment include time, dose, and route of application. Spots resulting from expression of recessives (RS), from cell killing (WMVS), and spots due to misdifferentiation (MDS) are distinguishable by location and color, and must be recorded separately. The spots test is relatively fast compared with some other whole-mammal tests, but requires more resources than do assays involving prokaryotes, lower eukaryotes and cell-culture systems. Major strengths of the spot test are it is an in vivo test; it monitors gene mutation end-points, as well as several types of chromosomal damage; and it provides ancillary information on cytotoxicity, embryotoxicity and teratogenicity of a compound. A positive result classifies a chemical as a potential carcinogen; to date all agents found positive have been carcinogens or have not be tested for carcinogenicity. A positive spot test will also indicate the possibility that inherited damage could be produced, which would indicate further germ-line mutagenicity studies. A negative test must be qualified by the possibility of a placental barrier. (3 Refs)

55. ALGINATE: A NEW REVERSIBLE GELLING MEDIUM FOR INVESTIGATING CELL TRANSFORMATION (MEETING ABSTRACT)

Roscoe JP, Owsianka AM

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Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

Previous investigations of the malignant transformation of rat brain cells by ethylnitrosourea have shown that tumorigenic cells form colonies in agar. Furthermore, pre-neoplastic cells which do not form colonies nevertheless survive, but in an essentially non-dividing state, for much longer (up to 10 weeks) than control cells. Investigation of this phenomenon has been hampered by the technical difficulties of long term maintenance and recovery of cells suspended in methocel or agar. We have developed alginate as an alternative suspending medium from which viable cells can be recovered by disrupting the cation dependent linkages with a chelating agent. A base layer of 0.6% agar is allowed to set and the appropriate concentration of calcium chloride solution placed on top. Cells suspended in 1% sodium alginate are immediately overlaid resulting in the formation of a gel as the calcium ions react with the alginate. Cells can be released by addition of EDTA and collected by centrifugation. The results using this medium show that 1) tumorigenic and non-tumorigenic cells can be distinguished by colony forming ability in alginate 2) the difference in viability of pre-neoplastic and control cells found in agar can be reproduced with the advantage that the recovery over several weeks can be quantitated. (1 Ref)

56. AN EVALUATION OF ASSAY PROCEDURES FOR DETECTION OF TUMOR PROMOTORS.

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Mutat Res; 98(3):377-387 1982

Direct cell culture assays, direct animal assays, and indirect assays for detection of tumor promoters are reviewed. Among the biological assays available for detection of tumor-promoting agents by means others than long-term carcinogenicity tests, those procedures that can determine phorbol ester activity and other substances active on mouse skin have been studied most intensively. When fibroblast cultures derived from individuals with hereditary adenomatosis of the colon and the rectum were treated with phorbol myristate acetate (PMA), they yielded cultures that could grow in soft agar and produce tumors in the anterior chamber of the eye of athymic mice. Experiments with oncogenic viruses and phorbol esters in cell culture systems show that phorbol esters can influence the neoplastic phenotype resulting from biological oncogenic as well as chemical stimuli. An enhancement of mutation frequency in V79 Chinese hamster cells was observed in cell culture with phorbol ester. PMA and other phorbol esters could reduce the recovery of 6-thioguanine-resistant mutants in a mixed culture of V79 cells in the presence of this purine derivative. A range of substances including promoters for rat liver (chlorinated aromatics), rat bladder (saccharin), and other organs also have been reported to have a blocking effect on metabolic cooperation. Studies indicated that the biochemical responses not directly implied in a causal manner to tumor promotion would require susbstantial validation to establish their usefulness as screening tools for tumor-promoting agents. (62 Refs)

57. PREDICTIVE ASSAYS FOR MUTAGENS AND CARCINOGENS.

Butterworth BE
Chemical Industry Inst. Technology, Research Triangle Park, NC
Scientific Considerations in Monitoring and Evaluating Toxicological Research. Gralla EJ, ed. Washington, D. C., Hemisphere Publishing Corporation, 221 pp., 1981.

General principles involved in the formulation of a testing program for mutagens and carcinogens and the evaluation of results are presented. Considerations in the selection of systems and evaluation of results are outlined for bacterial mutagenesis assays, mammalian cell culture mutagenesis assay, cell transformation assays, DNA damage assays, DNA repair assays, and whole-animal systems including classical cytogenetic techniques, sister chromatid exchange assays, dominant lethal assay, sperm morphology assay, and the recessive spot test. (22 Refs)

GENERAL REVIEWS AND OTHER RELATED STUDIES

58. THE ONCOGENIC CIRCLE CLOSES.

Rigby PW
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Nature; 297(5866):451-453 1982

Characterization of cellular oncogenes is reviewed. Oncogenes exhibit target specificity within a lineage. Recombinant DNA technics have been applied to the cloned human bladder carcinoma oncogene. The relationship between cellular oncogenes and proto-oncogenes (genes detected by transfection) has been studied. Retrovirus onc genes have been cloned and used to analyze DNA of NIH cells transformed by a variety of cellular oncogenes. The cloned human bladder carcinoma oncogene has been shown to be homologous to ras, the transforming gene of Harvey murine sarcoma virus. Mechanisms of oncogene activation and action are discussed. (19 Refs)

59. CHROMOSOMAL REARRANGEMENT AND CARCINOGENESIS.

Radman M, Jeggo P, Wagner R
Departement de Biologie Moleculaire, Universite Libre de Bruxelles, 76 rue des Chevaux, 1640 Rhode-St-Genese, Belgium
Mutat Res; 98(3):249-264 1982

Chromosomal rearrangement (CR) associated with carcinogenesis, CR in human cancer-prone syndromes, carcinogenic CR, induction of CR, role of CR in carcinogenesis, and mechanism of carcinogenesis were examined. To determine whether the ability to induce CR is a general property of carcinogens, 61 carcinogens (45 Ames test-positive, 16 Ames test-negative) were examined. Obtained data supported the hypothesis that the ability to induce CR is correlated with carcinogenesis. The association of CR with human and rodent cancers and with human cancer-prone systems further support the hypothesis. Also suggestive was the finding that DNA from non-malignant cells can transform other non-malignant cells, under conditions that may involve CR. Evidence suggesting that some DNA lesions can act as preferential sites for the initiation of DNA exchange is discussed. In addition, the results of several experiments suggested that carcinogens, at least radiation, can act epigenetically to induce recombinant activity. Apparently, carcinogens can act to induce CR by creating or revealing sites of DNA for recombination or by inducing or activating cellular systems resulting in a stimulation of recombination. The ploidy-change class of CR can allow either the amplification of genes, by increasing ploidy, or the expression of recessive genes, by decreasing ploidy. Thus all classes of CR may affect gene expression, and therefore, carcinogenesis. Proposal concerning some of the steps in carcinogenesis, implying that malignancy may be a result of the expression of cellular 'cancer genes' which are either not expressed or insufficiently expressed in normal cells because they are linked with a poorly transcribing control region, is presented. (57 Refs)

60. RELATIONSHIP OF DNA TERTIARY AND QUATERNARY STRUCTURE TO CARCINOGENIC PROCESSES.

Lipetz PD, Galsky AG, Stephens RE
Dept. Radiology, Ohio State Univ., Columbus, OH, 43210
Adv Cancer Res; 36:165-210 1982

DNA superstructure as studied in nucleoids (permeabilized and protein-depleted nuclei) and possible correlations between modification of the tertiary (supercoiling) and quaternary (supercoiled domains) levels of organization and carcinogenic processes are reviewed. Evidence that the nucleoid technique can be used to quantify extremely low levels of DNA strand breaks (less than 1/4.4 x 10(10) daltons of DNA) is discussed. Chromatin origins of DNA supercoiling; physiological relevance of decreased nucleoid DNA supercoiling; novobiocin and nalidixic acid as probes of DNA supercoiling; prokaryotic DNA supercoiling; and eukaryotic DNA superstructure are discussed. Crown gall tumorigenesis, chronic lymphocytic leukemia, 12-O-tetradecanoyl-phorbol-13-acetate-induced alterations of DNA superstructure in normal human cells and chromatin damage and repair are addressed. The relationship of DNA superstructure to the processes of carcinogenesis, carcinogenic promotion, and Z DNA is discussed. DNA superstructure studies may lead to a resolution of the conflict between the idea that neoplastic transformation results from altered informational flow from DNA (as in somatic mutation) and the concept that membrane-associated events lead to malignant transformation. DNA superstructure could be responsive to both levels of control. (211 Refs)

61. THE ROLE OF RADIATION AND CHEMICALS IN THE INDUCTION OF MUTATIONS AND EPIGENETIC CHANGES DURING CARCINOGENESIS.

Trosko JE, Chang CC
Dept. Human Development, Coll. Human Medicine, Michigan State Univ., East Lansing, MI, 48824
Adv Radiat Biol; 9:2-36 1981

The relationships between physical and chemical agents and their interactions and the triggering of 'regulatory dysfunction' are reviewed. The abnormal phenotype that is cancer, the multistage nature of carcinogenesis, and the classes of genetic and environmental agents affecting genetic initiation and promotion are discussed. Evidence supporting both the somatic mutation and epigenetic theories of carcinogenesis is reviewed, and an integrative model allowing for mutational and/or epigenetic mechanisms in progression of carcinogenesis is proposed. (255 Refs)

62. EXPRESSION OF EUKARYOTIC VIRAL AND CELLULAR GENES.

Pettersson RF, Kaariainen L, Soderlund H, Oker-Blom N
Dept. Virology, Univ. Helsinki, Helsinki, Finland
Expression of Eukaryotic Viral and Cellular Genes. London, Academic Press, 324 pp., 1981.

Recent advances in molecular virology, molecular genetics, and recombinant DNA research are combined in a discussion of expression of eukaryotic viral and cellular genes. Structure and expression of DNA virus genes are reviewed with respect to molecular analysis of adenovirus transformation, control of adenovirus messenger (m)RNA production by differential transcription and differential stability of mRNA, an early adenovirus glycoprotein and its association with transplantation antigens, the control of adenovirus early gene expression, and mutational analysis of regulatory elements of simian virus 40. Retrovirus genes are discussed with respect to OK 10 virus-transformed bone-marrow-derived cell line, the transforming insert in the Abelson murine leukemia virus genome, and DNA intermediates in the replication of retroviruses. RNA virus genes are discussed with respect to the genome of single-stranded messenger-sense RNA viruses, influenza virus, capped cellular RNAs, drift and shift of influenza A-type virus, vesicular stomatitis virus and host cell phosphoproteins, initiation of eukaryotic protein synthesis, alphavirus gene products, Semliki Forest virus, RNA containing heterogeneous 5'-terminal nucleotide sequences, and Semliki Forest virus defective interfering RNA using DNA copies. Eukaryotic genes are discussed with respect to structure, organization and developmental expression of chorion multigene families, gene amplification and methotrexate resistance, RNA-protein complexes precipitated by Lupus antibodies, promoter sequences, expression of cloned eukaryotic genes in microorganisms, human genomic DNA-encoding Pro-opiomelanocortin, and functional yeast minichromosomes containing centromeric DNA. (701 Refs)

63. MOLECULAR EPIDEMIOLOGY AND CARCINOGEN-DNA ADDUCT DETECTION: NEW APPROACHES TO STUDIES OF HUMAN CANCER CAUSATION.

Perera FP, Weinstein IB
Div. Environmental Sciences, Columbia Univ., New York, NY, 10032
J Chronic Dis; 35(7):581-600 1982

Techniques with potential usefulness in molecular cancer epidemiology are reviewed, with special emphasis placed upon a highly sensitive assay that detects covalent binding of the polycyclic aromatic hydrocarbon benzo(a)pyrene to human DNA. Benzo(a)pyrene has assumed considerable importance among chemical carcinogens because it has proven carcinogenic potency in a variety of species and tissues, it is ubiquitous in the environment, and there is extensive information regarding its metabolism and mode of action. Laboratory methods applicable to molecular cancer epidemiology include techniques to assess specific host factors that may influence susceptibility to carcinogens; assays that detect carcinogens in human tissues, cells, or fluids; assays at the cellular level of biologically effective doses of carcinogens; and methods to measure early biologic and biochemical responses to carcinogenic agents. Inherited and acquired host factors that may influence human susceptibility to carcinogens, methods for detecting and quantitating chemical carcinogens in human tissues or body fluids, markers for assessing the biologically effective dose of carcinogens in humans, potential markers for early biological and biochemical response to carcinogens in humans, and the immunoassay of benzo(a)pyrene-DNA adducts as an example of a promising marker in molecular cancer epidemiology are among topics discussed. (229 Refs)

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CHEMICAL CARCINOGENESIS

1. TOXICITY OF POLYBROMINATED BIPHENYLS (PBBS) IN DOMESTIC AND LABORATORY ANIMALS.
Damstra T, Jurgelski W, Posner HS, Vouk VB, Bernheim NJ, Guthrie J, Luster M, Falk HL
Natl. Inst. Environmental Health Sciences, Post Office Box 12233, Research Triangle Park, NC, 22709
Environ Health Perspect; 44():175-188 1982

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Davidson IW, Sumner DD, Parker JC
(c/o Parker) ECAO, Environmental Protection Agency, MD-52, Research Triangle Park, MD, 27711
Drug Chem Toxicol; 5(1):1-87 1982

3. FORMALDEHYDE IN PRESENT-DAY ENVIRONMENTAL TOXICOLOGY.
Beritic T, Kovac S, Dimov D
Odjel za profesionalne bolesti, Institut za medicinska istrazivanja i medicinu rada, Zagreb, Yugoslavia
Arh Hig Rada Toksikol; 32(4):363-395 1981
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4. HORMONES AS ETIOLOGICAL AGENTS IN NEOPLASIA.
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Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

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Zentralbl Bakteriol Mikrobiol Hyg [B]; 173(1/2):63-91 1981
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8. HISTORICAL OVERVIEW OF NITROSOUREA DEVELOPMENT.
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INSERM Symp; 19:3-11 1981

9. PATHOLOGY.
Goyer RA
Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC
JAMA; 247(21):2973-2975 1982

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10. IDENTIFYING THE HEALTH RISKS FROM VERY LOW-DOSE SPARSELY IONIZING RADIATION.
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Am J Public Health; 72(6):585-588 1982

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12. RADIOBIOLOGY OF RISK ESTIMATES IN MEDICAL IRRADIATION (MEETING ABSTRACT)
Rossi HH
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IN: 148th National Meeting of the American Association for the Advancement of Science, January 3-8, 1982, Washington, D.C American Association for the Advancement of Science 182 pp., 1982.

13. RADIATION-INDUCED VASCULAR INJURY AND ITS RELATION TO LATE EFFECTS IN NORMAL TISSUES.
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14. CURRENT CONCEPTS IN ULTRAVIOLET CARCINOGENESIS.
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Med Radiol (Mosk); 27(4):62-71 1982
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EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

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Dept. Pharmacology, Sch. Medicine, SJ-30, Univ. Washington, Seattle, WA, 98195

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TRANSFORMATION GENE STRUCTURE

1. A NOVEL CELL TRANSFORMATION WITH DNA-CONTAINING CYTOPLASMIC YABA TUMOR POXVIRUS.

Rouhandeh H, Vafai A
Lab. Molecular and Cancer Virology, Dept. Microbiology, Southern Illinois Univ., Carbondale, IL, 62901
Virology; 120(1):77-92 1982

Monkey kidney cells were morphologically transformed in vitro with uv-irradiated Yaba tumor poxvirus. Cell lines established were shown to be virus nonproducers and exhibited biological characteristics typical of transformed cells. These characteristics included increased saturation density, reduced serum requirements for growth, and ability to grow in soft agar. The morphological alterations of transformed cells were similar to Yaba virus-induced tumor cells and were characterized by loss of contact inhibition, multinucleated cells, and cytoplasmic lipid droplets. Southern blot hybridization revealed that sequences homologous to low-mol-wt viral DNA were present in the transformed cells. Yaba virus-specific antigens detected by immunofluorescence assays were found to be in the cyto-

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plasm of transformed cells. Four virus-specific proteins, with mol wt of 160,000, 140,000 107,000, and 74,000 daltons, were detected in transformed cells immunoprecipitated with sera from tumor-bearing monkeys. These results indicate that DNA-containing Yaba tumor virus, which replicates exclusively in the cytoplasm, is capable of inducing cell transformation in vitro. (Author abstract) (32 Refs)

2. T24 HUMAN BLADDER CARCINOMA ONCOGENE IS AN ACTIVATED FORM OF THE NORMAL HUMAN HOMOLOGUE OF BALB- AND HARVEY-MSV TRANSFORMING GENES.

Santos E, Tronick SR, Aaronson SA, Pulciani S, Barbacid M
Lab. Cellular and Molecular Biology, NCI, NIH, Bethesda, MD, 20205
Nature; 298(5872):343-347 1982

A transforming gene isolated from T24 human bladder carcinoma cells is closely related to the BALB murine sarcoma virus (MSV) onc gene (v-bas). This transforming gene is localized to a 4.6 kilobase pair (kbp) region and is expressed as a 1.2-kbp polyadenylated transcript, which contains v-bas related sequences. Moreover, antisera known to detect the immunologically related onc gene products of BALB- and Harvey-MSV recognized elevated levels of a related protein in T24 cells. The normal human homologue of v-bas was found to be indistinguishable from the T24 oncogene by heteroduplex and restriction enzyme analysis. These results imply that rather subtle genetic alterations have led to the activation of the normal human homologue of v-bas as a human transforming gene. (Author abstract) (48 Refs)

3. HUMAN DNA SEQUENCE HOMOLOGOUS TO THE TRANSFORMING GENE (MOS) OF MOLONEY MURINE SARCOMA VIRUS.

Watson R, Oskarsson M, Vande Woude GF
Lab. Molecular Oncology, NCI, NIH, Bethesda, MD, 20205
Proc Natl Acad Sci USA; 79(13):4078-4082 1982

We describe the molecular cloning of a 9-kilobase-pair BamHI fragment from human placental DNA containing a sequence homologous to the transforming gene (v-mos) of Moloney murine sarcoma virus. The DNA sequence of the homologous region of human DNA (termed humos) was resolved and compared to that of the mouse cellular homolog of v-mos (termed mumos). The humos gene contained an open reading frame of 346 codons that was aligned with the equivalent mumos DNA sequence by the introduction of two gaps of 15 and 3 bases into the mumos DNA and a single gap of 9 bases into the humos DNA. The aligned coding sequences were 77% homologous and terminated at equivalent opal codons. The humos open reading frame initiated at an ATG found internally in the mumos coding sequence. The polypeptides predicted from the DNA sequence to be encoded by humos and mumos also were found to be extensively homologous, and 253 of 337 amino acids were shared between the two polypeptides. The first five NH2-terminal and last two COOH-terminal amino acids of the humos gene product were in common with those of mumos. In addition, near the middle of the polypeptide chains, four regions ranging from 19 to 26 consecutive amino acids were conserved. However, we have not been able to transform mouse cells with transfected humos DNA fragments or with hybrid DNA recombinants containing humos and retroviral long terminal repeat (LTR) sequences. (Author abstract) (28 Refs)

4. DNA SEQUENCES REQUIRED FOR SPECIFIC AND EFFICIENT INITIATION OF TRANSCRIPTION AT THE POLYOMA VIRUS EARLY PROMOTER.

Jat P, Novak U, Cowie A, Tyndall C, Kamen R
Transcription and Nucleic Acid Chemistry Laboratories, Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Mol Cell Biol; 2(7):737-751 1982

The 5'-flanking sequences of the principle polyoma virus (Py) early promoter region was studied by the construction of deletion and substitution mutants. In vivo effects of certain mutations were measured by assay of the ability of DNAs to transform rat fibroblasts; effects of all mutations on the position and efficiency of in vitro initiation were measured with quantitative assays. A convenient internal control was the secondary Py early promoter region. Sequence requirements for efficient in vivo expression were different from those in vitro. DNA deletions between 200 and 400 base pairs (bp) before the principal cap sites severely inhibited in vivo expression measured as transformation ability, while in vitro transcription was not affected. Viable deletion mutants lacking the principal cap sites and the 'TATA' box were poor templates for in vitro transcription. In vitro analysis of other deletion mutants showed that specific sequences more than 46 bp before the cap sites were important. TATA box removal reduced in vitro transcriptional efficiency but did not alter initiation sites. Synthesis of transcripts with abnormal 5' termini did not occur in vitro until the sequence between the TATA box and the normal cap sites was also deleted. There was a nonspecific requirement for 90-100 bp of DNA 5' to the cap site for optimal transcription of DNA fragments in vitro. (73 Refs)

5. THE DETECTION AND MAPPING OF CONSERVED NUCLEOTIDE SEQUENCES BETWEEN THE GENOMES OF HUMAN PAPILLOMAVIRUS 1A AND BOVINE PAPILLOMAVIRUS 1 BY ELECTRON MICROSCOPE HETERODUPLEX ANALYSIS.

Croissant O, Testamiere V, Orth G
Unite des Papillomavirus, Institut-Pasteur, 25, rue du Docteur Roux, 75724 Paris, France
C R Seances Acad Sci [III]; 294(12):581-586 1982

The genome of papillomavirus (PV) is formed of about 8000 base pairs. In natural conditions, PV may cause epithelial or benign fibroepithelial tumors of the skin or mucosa which in certain cases can evolve toward malignancy. The virus only reproduces in keratinocytes in benign tumors. A fragment representing only 69% of the genome is required for PV transformation by bovine PV 1 (BPV 1). Electron microscope analysis of heteroduplex molecules revealed three regions of partial homology between the genomes of human papillomavirus 1a and BPV1. These regions represent about 25% of non-homologous bases and 13% of the genome length. The regions were mapped on viral DNA which allowed a reciprocal orientation of the physical maps of the two genomes. Two regions were located in the middle of the transforming fragment of BPV-1 DNA and the third region, which was located in an entirely different area, was in the region of the genome coding that was probably for a viral structural protein. (19 Refs) (In FRE)

6. THE CHANGES IN PROVIRAL CHROMATIN THAT ACCOMPANY MORPHOLOGICAL VARIATION IN AVIAN SARCOMA VIRUS-INFECTED RAT CELLS.

Chiswell DJ, Gillespie DA, Wyke JA
Amersham International, Amersham, Bucks, England
Nucleic Acids Res; 10(13):3967-3980 1982

The clone All of avian sarcoma virus B77-infected Rat-1 cells comprises both morphologically normal and morphologically transformed derivatives. Transformed subclones, in which virus-specific RNA is readily detectable, contain a provirus that is very sensitive to DNase I digestion of chromatin, and show DNase I hypersensitive sites at the 5' end of the provirus and in 5' flanking cell DNA. Normal subclones with no detectable virus-specific RNA, whether infected cells that have never been transformed or revertants derived from transformed cells, contain a provirus that is far more resistant to DNase I digestion. Moreover this provirus lacks hypersensitive sites at its 5' end, although DNase I hypersensitive sites are present in 5' flanking cell DNA. No DNase I hypersensitive sites were detected at the 3' end of the provirus in either normal or transformed clones. The pattern of cytosine methylation in the proviral restriction sites of the isoschizomers Msp I and Hpa II differed between transformed and revertant clones; the revertants show additional methylation at some CpG doublets. (Author abstract) (42 Refs)

7. THE GENETIC BASIS OF RETROVIRAL-INDUCED TRANSFORMATION.

Robinson HL, Vande Woude GF
Worcester Foundation Experimental Biology, 222 Maple Ave., Shrewsbury, MA, 01545
Curr Top Microbiol Immunol; 98:11-16 1982

The interaction of retroviruses with oncogenic sequences was studied in vitro and in vivo. In vitro studies with the Maloney sarcoma virus (MSV) indicated that the long terminal repeats (LTR) of MSV have transcriptional control sequences and structures that resemble insertion sequences. LTR enhanced transformation by an MSV DNA fragment containing the v-mos sequence (a viral homolog of the cellular c-mos sequence). Enhancement of transformation was accomplished either by directly linking the LTR and v-mos or by simultaneously transfecting a plasmid containing a single LTR with a plasmid containing v-mos. LTR may therefore enhance transformation by providing transcriptional control signals. LTR also activates transformation by c-mos. Transformation of cells by MSV apparently requires c-mos and LTR. Oncogenesis was studied in vivo by infecting K28 chickens with RAV-0 endogenous virus or with NTRE-7 (a nontransforming subgroup E recombinant of exogenous Pr-RSV-B and RAV-0 viruses). Of 58 chickens infected with RAV-0, none developed disease. Of 75 chickens infected with NTRE-7, 11 developed neoplasias (3 lymphomas, 2 fibrosarcomas, 2 carcinomas, 1 chondrosarcoma, and 3 osteopetroses). RAV-0 and NTRE-7 differ only in the immediate 3' sequences; therefore these sequences contain transcriptional controls for synthesis of viral messenger RNA that determine oncogenic potential in NTRE-7. Findings support a model of viral oncogenesis in which oncogenesis is controlled by the region of the viral genome that encodes control of transcription, and the type of neoplasia produced is determined by specific 3' oncogenic sequences. (16 Refs)

8. DEVELOPMENT OF APPROACHES TO MAP THE SARCOMA VIRUS-RELATED GENES.

Strauss EM
The Ohio State University, Columbus, OH
Diss Abstr Int [B]; 42(7):2709-B 1982

Previous work in this laboratory suggested that transcriptional activation and, perhaps, mutation of certain rat DNA sequences, which are related to the Kirsten murine sarcoma virus (K-MuSV) genome, may be required for carcinogenesis. To determine if gene activation and/or cellular transformation entailed any detectable physical alterations of the SV-related sequences, these sequences were examined in normal and transformed cells, by restriction enzyme and hybridization analyses. A method was developed for efficient production of virus-specific RNA components, which allowed direct isolation of viral RNA from serum-free culture medium, and rapid recovery of individual RNA species from high resolution sucrose gradients. After development of this new technology, another source of probe became available, a cloned DNA from a virus related to K-MuSV namely Harvey MuSV (H-MuSV). Sequences in K-MuSV cDNA were defined by comparison to H-MuSV DNA using hybridization analysis. Sections of H-MuSV DNA were then used as hybridization probes to represent portions of the K-MuSV genome. Viral DNA fragments representing the 5' (0.6-kb fragment) and the 3' (1.0-kb fragment) halves of the SV-related sequences hybridized with multiple bands in all Eco RI digested rat cell DNAs. Two bands are of the intensity expected for single copy DNA, while the other two bands hybridize more intensely. A preliminary model for the arrangement of the SV-related sequences is proposed. Two major subsets of the SV-related sequences are postulated with copies arranged in a tandem series in each subset. (no Refs)

9. CLONING OF DNA FRAGMENTS FROM THE LEFT END OF THE ADENOVIRUS TYPE 12 GENOME: TRANSFORMATION BY CLONED EARLY REGION 1.

Byrd PJ, Chia W, Rigby PW, Gallimore PH
Dept. Cancer Studies, Univ. Birmingham Medical Sch., Cancer Res. Campaign Lab., Birmingham B15 2TJ, England
J Gen Virol; 60(part2):279-293 1982

The human adenovirus serotype 12 (Ad-12) EcoRI-C DNA fragment (0 to 16.5 map units) was cloned in the plasmid vector pAT153. This cloned Ad-12 EcoRI-C DNA fragment was subcloned generating recombinant plasmids which contained the Ad-12 SalI-C fragment (0 to 10.3 map units), the Ad-12 HindIII-G fragment (0 to 6.8 map units) and the Ad-12 AccI-H fragment (0 to 4.7 map units). Thus, we constructed recombinant plasmids which contain Ad-12 DNA sequences which represent all or part of the virus transforming gene region. The capacity of the cloned Ad-12 EcoRI-C DNA fragment to transform rat cells in vitro was assessed using the focus assay on primary cultures of rat cells. The specific transforming activity of this recombinant plasmid was in the same range as that found for intact Ad-12 DNA. Transformed foci which were induced by the cloned Ad-12 EcoRI-C DNA fragment were established as cell lines and the presence of AD-12 DNA in these lines was demonstrated using the Southern blotting technique. (Author abstract) (47 Refs)

TRANSFORMATION GENE EXPRESSION AND REGULATION

10. ASSOCIATION OF THE TRANSFORMING PROTEINS OF ROUS, FUJINAMI, AND Y73 AVIAN SARCOMA VIRUSES WITH THE SAME TWO CELLULAR PROTEINS.

Lipsich LA, Cutt JR, Brugge JS
Dept. Microbiology, State Univ. New York at Stony Brook, Stony Brook, NY, 11794
Mol Cell Biol; 2(7):875-880 1982

Association of proteins of mol wt 90,000 (pp90) and of 50,000 (pp50) with transforming proteins of Fuijinami sarcoma virus (FSV) and Yamaguchi 73 sarcoma virus (Y73) is demonstrated. To determine whether the pp90 and pp50 coprecipitated with the transforming proteins encoded by FSV and Y73, [35S]methionine-labeled cell lysates were first analyzed by direct immunoprecipitation. Both serum from rabbits bearing tumors induced by Rous sarcoma virus and anti-pp19gag sera precipitated structural proteins from FSV and Y73, transformation-defective Rous sarcoma virus (RSV), and nondefective RSV lysates. Three transformation-specific proteins were precipitated by the TBR serum from RSV-transformed cells. The two proteins, pp90 and pp50, coprecipitated with pp60src as a consequence of a physical association with pp60src. Immunoprecipitates of Y73-and FSV-transformed cell lysates incubated with antiserum to pp19gag were also found to contain proteins which comigrated with the pp90 and pp50 proteins, which associate with pp60src in RSV-transformed cell lysates. The pp90 and pp50 proteins were not precipitated from lysates of cells infected with transformation-defective virus, which are detected in the src gene, nor from uninfected chicken cells. Results strongly suggested that the cellular proteins pp90 and pp50 may have a common role in the mechanism of transformation induced by the sarcoma-inducing viruses which encode tyrosine-specific kinases. (17 Refs)

11. IN VIVO TYROSINE PHOSPHORYLATIONS OF THE ABELSON VIRUS TRANSFORMING PROTEIN ARE ABSENT IN ITS NORMAL CELLULAR HOMOLOG.

Ponticelli AS, Whitlock CA, Rosenberg N, Witte ON
Dept. Microbiology, Molecular Biology Inst., Univ. California, Los Angeles, CA, 90024
Cell; 29(3):953-960 1982

The transforming gene product of the Abelson murine leukemia virus (A-MuLV) is a phosphoprotein encoded by combined viral and cellular sequences. Previous work has shown the existence of a serologically crossreactive normal cellular phosphoprotein called NCP150. We have utilized two-dimensional phosphopeptide mapping and phosphoamino acid analysis to compare the structures of NCP150 and wild-type and mutant forms of the A-MuLV protein labeled in vivo with 32P-orthophosphate. This analysis demonstrated cellular homology between NCP150 and wild-type A-MuLV protein, but a number of phosphorylation differences were seen. Among them, two specific tyrosine phosphorylations present in all transformation-competent Abelson proteins were not observed in NCP150. No other phosphotyrosine-containing peptides were detected. In addition, transformation-defective mutants isolated from either the P120 or P160 wild-type strain lack phosphotyrosine-containing peptides. Double-infection studies with such transformation-defective and transformation-competent A-MuLV strains show that Abelson viral proteins may be substrates for their own tyrosine-specific kinase activity in vivo. These observations suggest that the phosphotyrosine kinase activity of the abl region may be controlled, and may function, differently in its viral and cellular forms. (Author abstract) (33 Refs)

12. DETECTION OF A TRANSFORMING GENE PRODUCT IN CELLS TRANSFORMED BY MOLONEY MURINE SARCOMA VIRUS.

Papkoff J, Verma IM, Hunter T
Dept. Biology, University California, San Diego, La Jolla, CA, 92093
Cell; 29(2):417-426 1982

We identified, in cells transformed by Moloney murine sarcoma virus (M-MuSV clone 124), a protein encoded by the M-MuSV transforming gene, v-mos. An antiserum against a synthetic peptide corresponding to the C terminus of a protein predicted from the v-mos nucleotide sequence specifically recognizes a protein doublet of approximately 37,000 daltons from 35S-methionine-labeled M-MuSV 124-transformed producer cells. By peptide mapping, this protein is almost identical to the 37 kd in vitro translation product from the M-MuSV v-mos gene. Immunoprecipitates from 32P-labeled cells contain a single v-mos-specific phosphoprotein, which has at least six sites of phosphorylation containing phosphoserine. Pulse-chase experiments show that the lower band in the 35S-methionine-labeled doublet is the primary translation product, which is modified, probably by phosphorylation, to yield the upper band. A similar mos protein is immunoprecipitated from HT1-MuSV-transformed cells, but not from uninfected NIH/3T3 cells. These mos proteins are present at very low levels in transformed cell lines. Cells acutely infected with M-MuSV 124, however, transiently contain much higher levels of the mos protein. These high levels coincide with extensive cell mortality. (Author abstract) (55 Refs)

13. QUANTITATION OF A 55K CELLULAR PROTEIN: SIMILAR AMOUNT AND INSTABILILTY IN NORMAL AND MALIGNANT MOUSE CELL LINES.

Mora PT, Chandrasekaran K, Hoffman JC, McFarland VW
Macromolecular Biology Section, NCI, NIH, Bethesda, MD, 20205
Mol Cell Biol; 2(7):763-771 1982

Quantitative expression of a specific 55,000 mol wt (55K) cell protein was studied in two groups of mouse fibroblast (clonal) cells from two parental clones, one with high (HT), the other with low tumorigenicity (LT). From the LT clone, tumor lines and clones were obtained by selecting rare, spontaneously transformed highly tumorigenic (mutant) cells. Cells were labeled during exponential growth with 35S-methionine, and the 55K protein was immunoprecipitated with a monoclonal antibody and quantitated. There were low and approx equal amounts of 55K in cells (clones) with both low and high tumorigenicity from both groups of cells; there was no correlation between quantitative expression of 55K protein and cellular tumorigenicity. As shown previously, there was approx 10 to 20-fold more 55K protein in all simian virus 40 (SV40)-transformed T antigen-positive derivative clones. The T antigen-negative revertant tumor lines and clones obtained by an immunological in vivo selection method had low amounts of 55K protein, as in the parent cell before SV40 transformation. In all T antigen negative cells (including highly tumorigenic cells), degradation of the 55K protein was rapid, with a half-life of 15-60 min. The 55K protein was stable in all T antigen-positive cells (half-life greater than 10 hr). There was a very low, or an undetectable amount of the 55K protein in primary cells established from the tumors induced by highly tumorigenic cells. In contrast, primary cells obtained from early murine embryos had large amounts of (stable) 55K proteins. (30 Refs)

14. INDUCTION OF THE SYNTHESIS OF A 70,000 DALTON MAMMALIAN HEAT SHOCK PROTEIN BY THE ADENOVIRUS E1A GENE PRODUCT.

Nevins JR
Rockefeller Univ., New York, NY, 10021
Cell; 29(3):913-919 1982

We have attempted to determine whether any cellular genes are activated as a result of the action of the adenoviral E1A gene. The proteins synthesized in uninfected HeLa cells have been compared to those produced in early adenovirus infected cells. At least one protein, absent from uninfected HeLa cells, was synthesized in large amounts following adenovirus infection. This 70 kd protein was not synthesized in cells infected with the E1A mutant dl312, even when the multiplicity of infection with the mutant was such that the only viral gene not expressed was the E1A gene. Thus the induction of the 70 kd protein requires the expression of the viral E1A gene. The 70 kd protein was also induced by heat shock in uninfected cells. The same 70 kd protein is synthesized in 293 cells, a line of human embryonic kidney cells transformed by a fragment of adenovirus DNA. These cells constitutively express the E1A and E1B genes. (Author abstract) (22 Refs)

15. STRUCTURAL AND FUNCTIONAL STUDIES OF THE TRANSFORMING PROTEIN OF RECOVERED AVIAN SARCOMA VIRUSES.

Karess RE
The Rockefeller University, New York, NY
Diss Abstr Int [B]; 42(9):3543-B 1982

The transforming protein, p60src, of recovered avian sarcoma viruses (rASV) was examined in detail, and compared with the p60src from nondefective Schmidt-Ruppin Rous sarcoma virus (SR-RSV) and with the p60-src homologue of normal cells. The enzymatic properties of the proteins obtained from these three sources were compared, and were shown to have very similar protein kinase activities. Proteolytic analysis with Staphylococcus aureus V8 protease, and trypsin were used to demonstrate an overall structural homology between rASV p60src and SR-RSV p60src. Methionine- and phosphate-containing peptides were generally indistinguishable between rASV and SR-RSV. However, a few leucine-containing peptides were consistently found in each of 14 rASV isolates, and were absent from the map of SR-RSV p60src. These rASV-specific peptides could be detected in the map of endogenous p60c-src. Such unique peptides serve as genetic markers, and demonstrate that the new src gene of rASVs is derived from the cellular c-src gene by genetic recombination. Large fragments of p60src, generated by various proteolytic activities, were also analyzed by tryptic digestion. This permitted the partial ordering of the peptides within the intact protein. Certain structural polymorphisms were found among the rASV p60srcs. In each case the variation was confined to the amino terminal portion of the protein. In two cases it appeared that slightly more c-src information was acquired at the amino terminus than was true for the majority of rASV isolates examined. One of these had apparently also suffered a small deletion near the N-terminus, resulting in a net shortening of the protein of 56,000 daltons. Despite the structural variations in p60src, all rASVs could transform cells in culture and induce tumors at the site of injection. However, the 56k variant consistently produced only tiny growths which eventually regressed. Possible explanations for the observed heterogeneity of the amino terminal structure are discussed. In light of the common origin and structure or rASV p60src and cellular p60c-src it is proposed that only the relative abundance of the former (under viral transcriptional control), is the cause of neoplastic transformation in infected cells. (no Refs)

16. CHARACTERIZATION OF TUMORIGENIC PROTEINS.

Stitt DT
University of Illinois at Urbana-Champaign, Urbana, IL
Diss Abstr Int [B]; 42(6):2348-B 1982

The 17K, 84K, and 94K SV40 T antigens from SV40 permissive and transformed cells were analyzed by tryptic peptide mapping on ion exchange columns. The 48K and 55K nonviral antigens, proteins immunoprecipitable by SV40 T antibody from SV40 permissive and transformed cells, were compared to the SV40 large T antigen and to each other by tryptic peptide mapping. The 48K and 55K nonviral antigens are not degradation products of the SV40 T antigens and at most are only slightly related to the SV40 T antigens. The 48K and 55K nonviral antigens are slightly related to each other, sharing about 3 methionine containing tryptic peptides. Four SV40 transformed human cell lines, one SV40 transformed mouse cell line, and eight SV40 transformed human/mouse somatic cell hybrid cell lines were examined for the expression of nonviral antigens. Differences were found in the patterns of expression of the nonviral antigens among the human cell lines, between the human and the mouse cell lines, and between the human/mouse somatic cell hybrid cell lines and the human lines from which they were derived. By comparing the tryptic peptides fractionated on cation exchange columns of the nonviral antigens it was determined that: (1) The 48K nonviral antigen in human/mouse hybrids is encoded by a mouse chromosome. (2) The 52K nonviral antigen in the Balb IV-8 human/mouse hybrid is encoded by a mouse chromosome and is probably a precursor to the mouse 48K nonviral antigen. (3) The 55K nonviral antigen in the C57-VII-6 human/mouse hybird is encoded by a human chromosome; while in the Balb IV-8 human/mouse hybrid the 55K protein band is encoded by a human chromosome and probably by a mouse chromosome also. (4) If the gene encoding the human nonviral antigen is located on a single chromosome, it is located on human chromosome 7. (no Refs)

GENETIC AND OTHER HOST FACTORS WHICH MODULATE ONCOGENIC TRANSFORMATION

17. EFFECTS OF 12-O-TETRADECANOYLPHORBOL-13-ACETATE ON FIBROBLASTS FROM INDIVIDUALS GENETICALLY PREDISPOSED TO CANCER.

Antecol MH, Mukherjee BB
Dept. Biology, Center for Human Genetics, McGill Univ., Montreal, Quebec, H3A 1B1, Canada
Cancer Res; 42(9):3870-3879 1982

The purpose of the present study was to determine whether skin fibroblasts from individuals, either with an inherited predisposition to cancer or with genetic disorders usually associated with a high risk of cancer, can be oncogenically transformed in vitro by a tumor promoter alone. The effects of chronic and limited applications of 12-O tetradecanoylphorbol-

13-acetate (TPA) on several properties that are associated with transformation were examined using skin fibroblasts from individuals with polyposis coli, a familial cancer syndrome, xeroderma pigmentosum, Fanconi's anemia, and trisomy 21. The results of this study show that TPA treatment induces similar changes on cellular morphology, growth rate, saturation density, epidermal growth factor binding, and cytoskeleton in fibroblasts from both normal and genetically predisposed individuals. None of these cell lines, however, acquired anchorage-independent growth or unlimited growth potential in culture after chronic application of TPA. These observations suggest clearly that skin fibroblasts from individuals with either a genetic predisposition to or a high risk of cancer may not exist in a preneoplastic or 'initiated' state susceptible to oncogenic transformation by TPA alone and that the mechanism of genetically determined cancer induction may be different from that of chemical carcinogenesis. (Author abstract) (28 Refs)

18. DIFFERENTIAL SUSCEPTIBILITY OF HUMAN CELLS TO TRANSFORMATION BY MURINE AND AVIAN SARCOMA VIRUSES.

Rhim JS, Trimmer R, Huebner RJ, Papas Ts, Jay G
NCI, NIH, Bethesda, MD, 20205
Proc Soc Exp Biol Med; 170(3):350-358 1982

The susceptibility of human skin fibroblasts from patients with adenomatosis of the colon and rectum (ACR) and Gardner's syndrome and of human osteosarcoma clonal cells to Kirsten murine sarcoma virus (KiMSV) and Rous sarcoma virus (RSV) was investigated. Results obtained confirmed a previous report that skin fibroblasts from individuals genetically predisposed to colorectal cancer were preferentially transformed by KiMSV. The human osteosarcoma clonal cells infected with RSV showed altered morphology, increased growth rate, higher efficiency of colony formation in soft agar, growth of larger aggregates and growth in aggregate form above an agar base, and tumorigenicity in nude mice. The transformed cells produced neither RNA-dependent DNA polymerase nor type C virus particles; however, the transformed cells contained RSV CF antigen and a rescuable infectious virus. The transformed cells also contained an RSV transformation specific protein p60src-associated kinase activity. (22 Refs)

19. EFFECTS OF FEEDER LAYERS MADE OF HUMAN, MOUSE, HAMSTER, AND RAT CELLS ON THE CLONING EFFICIENCY OF TRANSFORMED HUMAN CELLS.

Namba M, Fukushima F, Kimoto T
Dept. Pathology, Kawasaki Medical Sch., Kurashiki, 701-01, Japan
In Vitro; 18(5):469-475 1982

The effect of feeder layers on cloning efficiency of transformed human cells was investigated. Embryonic human skin or lung fibroblasts; adult human skin fibroblasts; early passage cells from embryos of mouse, rat, and hamster; established mouse cell lines; 3T3 and 10T1/2 were used as feeder layers after they were lethally exposed to Co-60 gamma-rays at 3,000 rad. As test cells to study the effect of feeder layers on cloning efficiency, WI-38 CT-1 cells transformed in vitro by Co-60 gamma-rays and HGC cells cultured from a human gastric cancer were used. The effect of feeder layers on the cloning efficiency of the test cells was dependent on cell density of feeder layer cells, sources of the feeder layer cells, and kinds of test cells. An optimal density of feeder cells produced cloning efficiencies 3 to 15 times higher than in cultures without a feeder layer. Generally, high density of cells in feeder layers decreased the cloning efficiency of the test cells, presumably owing the contact inhibition of growth and depletion of essential nutrients by the feeder layer cells. Regarding the effect of the feeder layers made of human fibroblasts, there were no significant differences in population doubling levels; tissue origins of fibroblasts; or fibroblasts derived from normal individuals, patients with cancer, or with a genetically high familial incidence of cancer, hereditary adenomatosis of the colon and rectum. (Author abstract) (26 Refs)

EXPERIMENTAL MODULATION OF ONCOGENIC TRANSFORMATION

20. DIFFERENTIAL RESPONSES OF PRIMARY AND TRANSFORMED HAMSTER EPIDERMAL CELLS TO 12-O-TETRADECANOYLPHORBOL-13-ACETATE (TPA) (MEETING ABSTRACT).

Sina JF, Bradley MO, Diamond L, O'Brien TG
Merck Institute for Therapeutic Research, West Point, PA, 19486
Proc Am Assoc Cancer Res; 23:391 1982

We have asked whether primary and transformed hamster epidermal cells respond differently to the tumor promoter TPA with respect to ornithine decarboxylase (ODC) activity and parameters of cell growth. In primary epidermal cell cultures TPA (0.16 uM), but not fresh serum-containing medium, induced ODC; the combination of serum and TPA was no more effective than TPA alone. In four independently derived, transformed cell lines, the ODC response at low passage levels was similar to that observed in primary cultures. With passage, the lines acquired the ability to grow in soft agar or form tumors in newborn hamsters, and the addition of TPA and serum caused a synergistic induction of ODC activity. Studies on cell growth showed that the continued presence of promoter in primary cultures delayed the onset of log phase approx 24 hr, but did not alter the subsequent growth rate, the plateau density achieved, or the cellular morphology and size compared with controls. Transformed cell lines responded similarly, but without the delay in growth. Incorporation of [3H]thymidine in primary cells was inhibited by TPA added alone, but stimulated by fresh serum; serum plus TPA caused a greater and more sustained stimulation than that seen with serum alone. A similar pattern was seen in some transformed lines, but others showed no effect of TPA in the presence or absence of serum. (no Refs)

21. MECHANISMS OF ENHANCEMENT OF CELL TRANSFORMATION BY TUMOR PROMOTERS (MEETING ABSTRACT).

Hirakawa T, Kakunaga T, Sugimura T
National Cancer Institute, National Institutes of Health, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:394 1982

The object of this study is to know the relationship of the pleiotropic effects induced by tumor promoters to their enhancement of carcinogen-initiated cell transformation. The potency of promoters for enhancing the transformation was measured by exposing 3-methylcholanthrene-pretreated A31-1-1 cells (Balb/3T3 subclone) to promoters for 2 weeks and scoring the transformation 2 weeks thereafter. The relative potencies in enhancing transformation of dihydroteleocidin B (DHTB), teleocidin B (TV), phorbol-12,13-didecanoate (PDD), 12-O-tetradecanoyl phorbol-13-acetate (TPA), 4-O-methyl TPA, and phorbol were approximately 100:100:30:1: less than 0.01: less than 0.01. The early effects of promoters on the cells, ie, induction of DNA synthesis in Go-arrested cells, stimulation of arachidonic acid release from membrane, and inhibition of EGF (epidermal growth factor) binding to cell surface receptor, were equally induced by DHTB, TB, PDD, and TPA and were hardly induced by 4-O-methyl TPA and phorbol. When the metabolic inactivation of these promoters in the cultures was measured by analyzing the metabolites using thin layer chromatography or by assaying the biological activities remained, the relative resistancies of DHTB, TB, PDD, and TPA to the metabolic inactivation by the cells were in parallel with their transformation enhancing potencies. However, the accumulated amounts of the induced DNA synthesis and arachidonic acid release during 8 days of promoter exposure were not different between DHTB, PDD, and TPA. On the other hand, the accumulated inhibition of EGF binding by DHTB and PDD was markedly greater than by TPA. (no Refs)

22. TRANSFORMING GROWTH FACTORS AND TUMOR CELLS CONSTITUTE AN AUTOCRINE SYSTEM IN SERUM FREE MEDIA (MEETING ABSTRACT).

Ozanne B, Wigely C, Zack J, Kaplan PL
University of Texas Health Science Center at Dallas, Dallas, TX
Fed Proc; 41(3):855 1982

The growth of Kirsten murine sarcoma virus (K-MSV) transformed cells in serum free media is dependent upon the utilization of ectopically produced TGFs (transforming growth factor). The growth of CSG211 cells, a methyl cholanthrene transformed mouse salivary gland cell line, in serum free media is dependent upon epidermal growth factor (EGF) even though the cells produce a potent TGF. After K-MSV transformation CSG211 cells become EGF independent and produce a TGF which replaces EGF in the serum free growth of CSG211 cels. The biochemical properties of the TGFs will be presented. These results suggest that TGFs play a role in both viral and chemical carcinogenesis. When TGFs are added to semi-solid media normal cells are rendered anchorage independent (AI). The ability of TGFs to elicit AI growth depends upon the cells inherent sensitivity to the TGF. Using a series of subclones of rat-1 cells we found some clones were resistant to TGF induced AI growth, while other clones were very sensitive to TGFs. The sensitive clones were also rendered AI by EGF which is not normally thought of as a TGF. The resistant clones are also resistant to transformation by K-MSV, Abelson murine leukemia virus and simian virus 40. Together the results suggest that transformation results from a combination of TGF production and an increase in sensitivity to the ectopically produced TGFs. (no Refs)

23. ISOLATION OF TRANSFORMING GROWTH FACTORS FROM HUMAN TUMOR CELLS (MEETING ABSTRACT).

Frolik CA, Dart LL, Sporn MB
National Institutes of Health, Bethesda, MD, 20205
Fed Proc; 41(3):855 1982

Transforming growth factors (TGFs) are low molecular weight proteins that are able to confer anchorage-independent growth on normal cells in soft agar. These factors have been found in the culture medium of several human tumor cell lines. Acid-ethanol extraction of human tumor cells [HeLa, rhabdomyosarcoma (A673) and melanoma (A2058)] has now also, demonstrated the presence of these proteins intracellularly. Gel filtration chromatography of the intracellular TGFs on Bio Gel P30 in 1 M acetic acid indicates two regions of activity with apparent molecular weights of 7 to 12K and 13 to 20K. Further purification by reverse-phase high-pressure liquid chromatography separates the proteins into at least two classes of TGFs. One class, that elutes from the column prior to epidermal growth factor (EGF), competes with EGF for cell membrane receptors and has soft agar colony forming activity that is not potentiated by EGF. The second class of TGFs is eluted from the column after EGF, does not compete with EGF for receptor binding, and has colony forming activity that is markedly potentiated by EGF. Initial experiments also indicate that acid-ethanol extracts of normal tissues contain low molecular weight compounds that will inhibit the action of TGF. The biological significance of these compounds is currently being investigated. (1 Ref)

24. ISOLATION OF A NEW CLASS OF TRANSFORMING GROWTH FACTORS FROM SARCOMA VIRUS TRANSFORMED CELLS (MEETING ABSTRACT).

Chua CC, Ladda RL
The Milton S. Hershey Medical Center, Hershey, PA, 17033
Fed Proc; 41(3):491 1982

Kirsten-sarcoma virus transformed rat kidney cells (KNRK) were found to secrete a group of transforming growth factors (TGFs). Conditioned medium for KNRK cells were collected, concentrated, dialyzed against 50 mM NaCl and 50 mM phosphate buffer (pH 7.2) and layered onto a Sephadex G-200 column. The transforming activity was assayed by the promotion of normal rat kidney cells (NRK) to form colonies on soft agar. The most active materials were separated in a region corresponding to the size of RNase A on a Sephadex G-200 column. Upon SDS (sodium dodecyl sulfate) gel electrophoresis, the active fractions could be resolved into four bands with apparent molecular sizes ranging from 13,000 to 17,500 daltons. This transforming activity was absent in the conditioned medium of NRK cells. In contrast to the TGFs previously isolated by De Larco and Todaro and Ozanne, Fulton and Kaplan, our TGFs did not compete with I125-EGF for EGF cell surface binding sites and did not stimulate the phosphorylation of EGF receptors on isolated NRK cell membranes. In addition, unlike the TGFs isolated by Roberts et al, EGF did not potentiate the transforming activity of our TGFs. The TGFs isolated under neutral conditions have markedly different charactristics compared to those isolated at acidic pH. It is apparent that TGFs show significant heterogeneity. (no Refs)

25. CHARACTERIZATION OF TWO CLASSES OF TRANSFORMING GROWTH FACTORS FROM MURINE SARCOMA VIRUS (MSV) TRANSFORMED CELLS (MEETING ABSTRACT).

Anzano MA, Roberts AB, Sporn MB
National Institutes of Health, Bethesda, MD, 20205
Fed Proc; 41(3):491 1982

Transforming growth factors (TGFs) are low molecular weight (6-20K), acid stable polypeptides that confer a malignant phenotype on non-neoplastic cells. Cellular TGFs were isolated from MSV-transformed 3T3 cells by acid/ethanol extraction and Bio-Gel P-30 chromatography. TGF activity, which is measured by the ability to induce anchorage independent growth of normal cells in soft agar, can be resolved into two classes using reversed-phase high performance liquid chromatography on a uBondapak C18 column with a gradient of acetonitrile containing 0.1% trifluoroacetic acid. Class I TGF elutes at 31% acetonitrile, competes for epidermal growth factor (EGF) membrane receptors, and forms relatively small colonies (850-3100 um2). Class II TGF elutes at 37% acetonitrile, does not compete for EGF membrane receptors, and requires EGF in order to induce large colony formation (greater than 3100 um2) in the soft agar assay. The potentiation of the activity of class II TGF by EGF or polypeptides that interact with the EGF receptor is specific; class I TGF shows this property, but insulin, insulin-like growth factor, platelet-derived growth factor and nerve growth factor do not. Characterization of the biological and chemical properties of these two classes of TGFs and their cooperative interactions are being investigated. (no Refs)

26. CHARACTERISTICS OF A PLATELET DERIVED GROWTH FACTOR (PDGF) THAT STIMULATES HUMAN TUMOR COLONY FORMATION (MEETING ABSTRACT).

Cowan DH, Quinn PG
St. Luke's Hospital, Cleveland, OH, 44104
Proc Am Assoc Cancer Res; 23:161 1982

The characteristics of a growth factor from platelets that stimulates human tumor colony formation were defined and compared to those of the factor(s) that stimulate non-transformed and SV/40-virus transformed 3T3 fibroblasts (3T3 and SV3T3 cells). Human tumor cells were grown in a 2-layer soft agar culture system. 3T3 and SV3T3 cells were grown in monolayer cultures. The proteins in the lysate were separated by gel filtration on Sephadex G-100 and Sephacryl S-200 and by chromatofocusing. Growth promoting activity (GPA) for 3T3, SV3T3, and tumor cells was non-dialyzable, stable at 56C for 30 min, inactivated by heating at 70C or 90C for 30 min and destroyed by periodate. GPA for tumor cells and 3T3 cells was stable at 100C for 2.5 min and decreased 75% and 62%, respectively, at 100C for 5 min. GPA and SV3T3 cells decreased 62% at 100C for 2.5 min and was absent after 100C for 5 min. Trypsin decreased GPA for tumor cells, 3T3 cells, and SV3T3 cells by 60%, 37%, and 67%, respectively. The isoelectric points of proteins with GPA for all cell lines were 7.0-8.0. The data indicate that the properties of the platelet protein(s) having GPA for human tumor cells differ from those of platelet proteins that stimulate 3T3 and SV3T3 cells. Platelets produce several proteins with GPA having distinctive target cell specificity. (no Refs)

27. INFLUENCE OF GROWTH FACTORS ON PROLIFERATION OF NORMAL AND CHEMICALLY TRANSFORMED RAT ESOPHAGEAL EPITHELIAL CELLS (MEETING ABSTRACT).

Stoner GD, Babcock MS
Department of Pathology, Medical College of Ohio, Toledo, OH, 43699
Proc Am Assoc Cancer Res; 23:162 1982

The proliferative response of normal (N) and N-nitrosomethylbenzylamine-transformed (T) rat esophageal epithelial cells to various growth factors was compared. We have so far determined the effects of several concentrations of dialyzed fetal bovine serum, epidermal growth factor (EGF), 12-O-tetradecanoylphorbol-13-acetate (TPA) and Ca++ on the clonal growth of N and T cells. The cells were seeded into 60 mm dishes and, after 5-7 days, the colonies were fixed, stained and the number cells per colony counted. Growth responses of N and T cells were compared by determining the number of population doublings per day per concentration of growth factor. For optimum clonal growth, N cells required four times as much serum as T cells. Moreover, N cells required serum for clonal growth whereas T cells grew in serum-free medium. EGF did not stimulate the growth of either N or T cells. The growth of T cells was not influenced by TPA whereas that of N cells was inhibited by as little as 0.3 ug/ml. Both N and T cells required a minimum of 10(-5) M Ca++ for clonal growth and reached optimum growth at 10(-4) M. N cells were stimulated to differentiate into keratinizing epithelial cells in medium containing 10(-3) M Ca++ and T cells were not. These data suggest that the difference in serum requirement for clonal growth of N and T cells is due to factors other than EFG and Ca++. (no Refs)

28. A PROBABLE MECHANISM FOR SYNERGISTIC EFFECT IN CHRYSOTILE AND BAP INDUCED TRANSFORMATION (MEETING ABSTRACT).

Chang MJ, Singh NP, Hart RW
National Center for Toxicological Research, Jefferson, AR, 72079
Proc Am Assoc Cancer Res; 23:199 1982

It is generally believed that the initial step of chemically induced cellular transformation is the fixation of DNA damage(s). Using a normal human skin fibroblast cell culture system, we investigated: 1) the cytotoxic effect of chrysotile asbestos; 2) thymidine incorporation, and 3) cellular uptake of BaP (benzo(a)pyrene) under the influence of asbestos. We observed: 1) chrysotile asbestos (10 ug/ml) exerted cytotoxicity at a cell density below confluency; 2) chrysotile treatment enhanced thymidine incorporation from the first to the fourth day post-treatment both in the presence or absence of BaP; 3) BaP uptake was enhanced in the culture simultaneously treated with asbestos. The preliminary findings indicate that protein and RNA binding of BaP was enhanced in the presence of chrysotile asbestos. Based on the data collected, we suggest that in the event of co-exposure of chrysotile asbestos and BaP, more DNA damage will result, that thymidine incorporation will be enhanced and is indicative of increased levels of DNA replication thereby leading to the fixation of genetic damage. (no Refs)

29. THE ROLE OF ANEUPLOIDY INDUCTION IN DIETHYLSTILBESTROL-INDUCED CELL TRANSFORMATION (MEETING ABSTRACT).

Barrett JC, Tsutsui T, Cummings T, Wong A, McLachlan JA
National Institute of Environmental Health Sciences, Research Triangle Park, NC, 27709
Proc Am Assoc Cancer Res; 23:129 1982

Gene mutations, changes in chromosome structure (aberrations) and chromosome number (aneuploidy) are possible types of genetic changes in neoplastic transformation. We reported that diethylstilbestrol (DES) induces morphological and neoplastic transformation of Syrian hamster embryo (SHE) cells in culture without induction of measurable gene mutations at two loci. We have now examined whether DES induces chromosomal alterations in asynchronous and synchronous cultures of SHE cells at doses which induce cell transformation. DES (0.01-1.0 ug/ml) induced significant levels of aneuploidy but not chromosome aberrations in asynchronous cultures. The majority (90-95%) of metaphases from control cultures had a diploid number of chromosomes, but 4-9% were polyploid and 1-2% were aneuploid around the diploid number. Highly synchronized cultures were treated with 1 ug/ml DES for 3 hr periods during different phases of the cell cycle. Cell transformation occurred in cultures treated in mitosis but not in those treated in early or late S phase. Aneuploidy induction also occurred in cultures treated in mitosis. No increase in chromosome aberrations was observed in any of the treated groups.

Malignant cell lines derived from DES treated cultures were aneuploid with near diploid chromosome numbers. These data along with the observations of aneuploid DNA content in dysplastic lesions of offspring of women exposed to DES suggest that induction of aneuploidy may be important in the carcinogenicity of DES. (1 Ref)

BIOCHEMICAL AND MOLECULAR BIOLOGICAL STUDIES OF THE TRANSFORMED PHENOTYPE

30. PURIFICATION OF A TYROSINE-SPECIFIC PROTEIN KINASE FROM ROUS SARCOMA VIRUS-INDUCED RAT TUMOR.

Blithe DL, Richert ND, Pastan IH
Lab. Molecular Biology, NIH, NCI, Bethesda, MD, 20205
J Biol Chem; 257(12):7135-7142 1982

We have identified a tyrosine kinase activity present in tumors which were raised in rats by subcutaneous injection of Rous sarcoma virus-transformed rat cells (SR-NRK). This kinase phosphorylates tyrosine on the heavy chain of IgG from tumor-bearing rabbit (TBR) sera specific for the src gene product, pp60src. Using TBR-IgG phosphorylation as an assay, we have purified this kinase over 7,200-fold. The purification procedure involves detergent extraction of tumors followed by sequential column chromatography on hydroxylapatite, DEAE-Sephacel, oligodeoxyadenosine-cellulose, an affinity column prepared from TBR-sera, and Sephacryl S-200. The IgG kinase activity behaves as a molecule of apparent Mr = 54,000 on Sephacryl S-200 molecular sieve chromatography. Analysis of the Sephacryl fractions by SDS-PAGE indicates that a major Coomassie blue-stained band with an apparent Mr = 54,000 (p54), co-elutes with the peak of kinase activity. From 600 g of tumors, approx 200 ug of p54 are obtained. We have four types of evidence which show that p54 is related to pp60src. (1) Purified p54 is capable of undergoing endogenous phosphorylation in the presence of [gamma-32P]ATP producing a 32P-labeled pp54 polypeptide which is specifically immunoprecipitated by TBR-sera and contains only phosphotyrosine. (2) Purified p54 competes with 32P labeled pp60src for binding to TBR-IgG, indicating a degree of purification over starting material which agrees very well with the results obtained by the IgG kinase assay. (3) V8 protease digestion of pp60src and p54 suggests that they share a common 26,000 fragment. (4) Antibodies to partially purified p54 specifically precipitate pp60src from Rous sarcoma virus-transformed chicken cells. (Author abstract) (45 Refs)

31. CHANGES IN THE RELATIVE PROPORTION OF TRANSFORMATION-SENSITIVE POLYPEPTIDES IN GIANT HELA CELLS PRODUCED BY IRRADIATION WITH LETHAL DOSES OF X-RAYS.

Bellatin J, Bravo R, Celis JE
Medical Res. Council Lab. Molecular Biology, Hills Road, Cambridge, England
Proc Natl Acad Sci USA; 79(14,part1):4367-4370 1982

Irradiation of HeLa cells with 1,100 rad (1 rad = 0.01 J/kg = 0.01 Gy) of x-rays yielded a pure population of giant cells 5-7 days after irradiation. These cells do not divide but go through an intermittent DNA synthetic phase. The population of giant cells in S phase (8%) is considerably lower than that of control asynchronous HeLa cells (30%), but 80% of the giant cells go through S phase as determined by 48-hr labeling with [3H]thymidine. Previous studies with high-resolution two-dimensional gel electrophoresis identified 58 [35S]methionine-labeled polypeptides common to human epithelial amnion cells and lung fibroblasts, whose rate of synthesis is sensitive to neoplastic transformation. These polypeptides also have been identified in HeLa cells and other transformed human cells such as Detroit 98, Chang liver, F1-amnion, and WISH-amnion. After irradiation of HeLa cells and giant cell formation, the relative proportions of most of the transformation-sensitive polypeptides (43 of 47) reverted to levels similar to those observed in non-tumorigenic cells. This suggests that their relative proportions are dependent on the growth properties of the cells. In particular, the relative proportions of three polypeptides (designated 12g and 60d1 in isoelectric focusing and 27b in nonequilibrium pH gradient electrophoresis) were not affected, indicating that their reduced amounts in transformed cells could reflect a fundamental change that develops during transformation. (Author abstract) (17 Refs)

32. IDENTIFICATION AND CHARACTERIZATION OF A 200,000 DALTON TUMOR ANTIGEN OF AVIAN SARCOMA VIRUS TRANSFORMED BALB/C CELLS (MEETING ABSTRACT).

Parsons SJ, McCarley DJ, Parsons JT, Benjamin DC
University of Virginia, Charlottesville, VA, 22901
Fed Proc; 41(3):555 1982

BALB/c bearing mice tumors induced by avian sarcoma virus (ASV) produce antibodies which immunoprecipitate the viral transforming protein, pp60src, and in some cases, antibodies to phosphoproteins with Mr ranging from 110 to 250 kd. Monoclonal antibodies were produced and used to determine whether these phosphoproteins either play a role in tumor rejection or are associated with pp60src, a known kinase. One monoclonal antibody specifically immunoprecipitates a major polypeptide of 200 kd and two minor polypeptides of 18 and 15 kd. The 200 kd peptide (p200) is found in both normal and transformed mammalian cell lines and chicken embryo fibroblasts (CEF). P200 from normal CEF appears to be slightly smaller in size and either less abundant or less highly phosphorylated than its transformed counterpart. Immunoaffinity purified ASV-BALB/c extracts contain these three polypeptides which, along with several other minor proteins, become phosphorylated during a cyclic nucleotide independent 'autophosphorylation' reaction. (no Refs)

33. BIOCHEMICAL ANALYSIS OF MURINE LEUKEMIA VIRUS-INDUCED TRANSFORMED AND ATYPICAL VIRAL BUDDING FORMS IN UC1-B MOUSE FIBROBLASTS.

Hann SR
University of California, Riverside, CA
Diss Abstr Int [B]; 42(10):4045-B 1982

In an effort to explain the MLV-induced transformation of UC1-B cells, most of the biochemical factors which are known to cause transformation were tested. The expression of the MoMSV transforming gene, v-mos, and the cellular transforming gene c-mos, was quantitated using defined complementary DNA 'probes': specific for the sequences common to Moloney MLV and MSV, and the transforming gene unique to Moloney MSV. Sensitive 'Dot blot', 'Northern blot' and solution hybridization analyses with these 'probes' demonstrated that v-mos and c-mos transforming sequences are not expressed in MLV-infected UC1-B cells. 'Southern blot' analyses of UC1-B genomic DNA restriction fragments were performed with the probes, and revealed no rearrangement or amplification of cellular c-mos sequences. In addition, the possibility of an increase in the normally small amounts of p60src-related and p21-related transforming proteins was examined by measuring with relative amounts of phosphotyrosine and the GDP-binding activity immunologically related to Harvey MSV p21 protein in UC1-B cells. These experiments indicated no increase in the amounts or activities of these transforming proteins. (no Refs)

34. THE EXPRESSION OF ALPHA-FETOPROTEIN AND ALBUMIN GENES IN RAT LIVER DURING CHEMICAL CARCINOGENESIS.

Schwartz CE, Gabryelak T, Smith CJ, Taylor JM, Chiu JF
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Biochem Biophys Res Commun; 107(1):239-245 1982

The expression of alpha-fetoprotein (AFP) and albumin genes in neoplastic and preneoplastic livers of Fischer rats treated with the hepatocarcinogen 3'-methyl-4-dimethylaminoazobenzene (MDAB) was investigated. The concentration of AFP started to increase in the serum of rats shortly after the initiation of feeding with MDAB (0.06% of the diet). It reached a peak at about 40 days and then decreased dramatically. After 164 days of treatment, serum levels of AFP increased markedly concomitant with the appearance of palpable liver tumors. The final permanent elevation of AFP was associated with the appearance of malignant cells. There was little if any change in the serum albumin concentrations in rats treated with MDAB. Synthesis of AFP in livers of MDAB-treated rats was found to increase in parallel with AFP serum concentrations. Biosynthesis of albumin showed no changes during hepatocarcinogenesis. These results indicate alteration in the control of gene expression during neoplastic transformation. (29 Refs)

35. CYTOTOXICITY AND DNA CROSSLINKING IN NORMAL AND TRANSFORMED HUMAN CELLS EXPOSED TO 1-(2-FLUOROETHYL)-3-CYCLOHEXYL-1-NITROSOUREA (FCNU) (MEETING ABSTRACT).

Sharkey NA, Erickson LC, Kohn KW, Oliverio VT
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Proc Am Assoc Cancer Res; 23:642 1982

FCNU, the fluoro analogue of CCNU, is as active as CCNU (lomustine) or other chloroethylnitrosoureas (CNU) against murine tumors. It differs from the CNU's, however, in that it produces much less DNA interstrand crosslinking (ISC). We have recently reported that ISC and cytotoxicity induced by CNU in human tumor cell depend on the Mer (methylation repair) phenotype. We now report the effects of FCNU on ISC and cytotoxicity in normal human fibroblasts (IMR-90) (Mer+) and SV-40 transformed human fibroblasts (VA-13) (Mer-). In cytotoxicity experiments, twice the drug concentration was required to effect a similar cell kill in IMR-90 as compared to VA-13. When the cell lines were analyzed by alkaline elution, comparable levels of DNA-protein crosslinking (DNP) were observed in both cell lines immediately after drug exposure, (DNP) increased in both lines over the next 24 hours, and decreased slowly in the subsequent 48 hour period. DNA interstrand crosslinking was detected in VA-13 but not in IMR-90 cells. However, unlike the chloroethylnitrosoureas which produce DNA interstrand crosslinks in the 6-12 hour period following drug treatment, interstrand crosslinks produced by FCNU in VA-13 cells were not detected until 48 hours after drug exposure. FCNU inhibited the proliferation of VA-13 cells as early as 24 hr after treatment, ie, before ISC was detected. (1 Ref)

CELL SURFACE PHENOMENA OF TRANSFORMATION

36. CODISTRIBUTION OF HEPARAN SULFATE PROTEOGLYCAN, LAMININ, AND FIBRONECTIN IN THE EXTRACELLULAR MATRIX OF NORMAL RAT KIDNEY CELLS AND THEIR COORDINATE ABSENCE IN TRANSFORMED CELLS.

Hayman EG, Oldberg A, Martin GR, Ruoslahti E
Cancer Res. Center, La Jolla Cancer Res. Foundation, La Jolla, CA, 92037
J Cell Biol; 94(1):28-35 1982

We used antibodies raised against both a heparan sulfate proteoglycan purified from a mouse sarcoma and a chondroitin sulfate proteoglycan purified from a rat yolk sac carcinoma to study the appearance and distribution of proteoglycans in cultured cells. Normal rat kidney cells displayed a fibrillar network of immunoreactive material at the cell surface when stained with antibodies to heparan sulfate proteoglycan, while virally transformed rat kidney cells lacked such a surface network. Antibodies to chondroitin sulfate proteoglycan revealed a punctate pattern on the surface of both cell types. The distribution of these two proteoglycans was compared to that of fibronectin by double-labeling immunofluorescent staining. The heparan sulfate proteoglycan was found to codistribute with fibronectin, and fibronectin and laminin gave coincidental stainings. The distribution of chondroitin sulfate proteoglycan was not coincidental with that of fibronectin. Distinct fibers containing fibronectin but lacking chondroitin sulfate proteoglycan were observed. When the transformed cells were cultured in the presence of sodium butyrate, their morphology changed, and fibronectin, laminin, and heparan sulfate proteoglycan appeared at the cell surface in a pattern resembling that of normal cells. These results suggest that fibronectin, laminin, and heparan sulfate proteoglycan may be complexed at the cell surface. The proteoglycan may play a central role in the assembly of such complexes since heparan sulfate has been shown to interact with both fibronectin and laminin. (Author abstract) (43 Refs)

37. ONCOVIRAL PROTEINS AS CELLULAR ANTIGENS.

Fleissner E, Snyder HW
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Curr Top Microbiol Immunol; 98:37-80 1982

The immunological recognition of proteins encoded by oncoviruses and the biological consequences of recognition are reviewed. Virally produced proteins include structural proteins of the virion, variants of these proteins that do not reside on the virions, and proteins that are coded by cellular genes that have become incorporated into the oncoviral genome. The last-mentioned type of protein can produce malignant transformation. Many viral proteins are found on the cell surface membrane and therefore act as antigens. As antigens, the proteins provide a target for immune response by the host. The immune response may be useful for in vitro serological analysis. The murine system has provided a model for study of immune response by the host to virion structural proteins and the expression of endogenous viral proteins in various hematopoietic cell lineages. The feline system has been a model for assessment of host responses to virally-induced malignancy. The feline system has produced the best evidence that an immune response by the host to viral transformation antigens can be decisive in rejection of a tumor and indicative of the incidence of a tumor in a population. Discussion emphasizes recognition in the host species from which particular viruses were derived. Only C-type viruses are discussed. (400 Refs)

38. DETECTION OF POLYOMA-VIRUS-INDUCED TUMOR ANTIGEN(S) BY MACROPHAGE MIGRATION INHIBITION.

Szigeti R, Dalianis T, Klein G, Ito Y, Magnusson G
Dept. Tumor Biology, Karolinska Inst., S 104 01 Stockholm, Sweden
Int J Cancer; 30(1):69-74 1982

We have applied the macrophage migration inhibition assay to study cell-mediated immune responses to antigens of polyoma-virus-transformed cells. Macrophages from polyoma-virus-immunized mice, but not from control mice, showed significant migration inhibition when exposed to extracts of polyoma-virus-induced mouse and rat transformed cells. Extracts of non-polyoma-induced tumors had no such effect. (Author abstract) (31 Refs)

39. GANGLIOSIDE GM1 SENSITIZES TUMOR CELLS TO GROWTH INHIBITORY GLYCOPEPTIDES.

Kinders RJ, Rintoul DA, Johnson TC
Div. Biology, Kansas State Univ., Manhattan, KS, 66506
Biochem Biophys Res Commun; 107(2):663-669 1982

A glycopeptide prepared from the surfaces of cerebral cortex cells of Swiss albino mice by mild proteolysis inhibits cellular protein synthesis in normal but not transformed cells. Treatment of C3H mouse fibrosarcoma 1316 cells with the glycopeptides resulted in only a limited degree of inhibition of cell protein synthesis compared to polyoma virus-transformed baby hamster kidney cells. The previously described possible role of ganglioside GM1 as a receptor for a number of glycoproteins with physiological activity suggested that the insensitivity of 1316 cells to the glycopeptide growth inhibitor (GGI) might be due to insufficient levels of GM1 in the cell surface membrane. When 1316 cells were incubated with GM1 under conditions in which the ganglioside is incorporated into the cells, the cells became sensitive to GGI. In parallel studies with ceramide, there was no change in 1316 sensitivity. When 1316 cells were incubated with GM1 for 18 hr, they appeared to metabolize GM1 to simpler gangliosides and lost their sensitivity to the glycopeptide inhibitor. (17 Refs)

40. ASSOCIATION OF SV40 LARGE TUMOR ANTIGEN AND CELLULAR PROTEINS ON THE SURFACE OF SV40-TRANSFORMED MOUSE CELLS.

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Houston, TX, 77030
Virology; 120(1):1-17 1982

A cellular protein with a mol wt of about 53,000 (53K) and histocompatibility antigens (mouse H-2 antigens) have been reported to be associated with viral-specified proteins in transformed cells. We investigated whether such associations could be detected on the surface of SV40-transformed mouse cells. A differential immunoprecipitation technique was adapted so that surface-associated antigens could be detected independently from intracellular antigens. The precipitated proteins were eluted and analyzed by SDS-polyacrylamide gel electrophoresis. Reconstruction experiments established that SV40 large T antigens (T-ag) released from the nucleus during the extraction procedure was not combining with free antigen-binding sites on antibodies bound to the cell surface in the external reaction, that nuclear unbound T-ag was not exchanging with bound surface antigen during extraction, and that the surface reaction was not due to nuclear T-ag released from dead cells and nonspecifically adsorbed onto the surface of living cells. It appears that SV40 large T-ag and cellular 53K protein are associated on the surface as well as within SV40-transformed mouse cells. In contrast, no detergent-stable complex between T-ag and mouse H-2 antigens was detected on the transformed cells. The possibility that molecular interactions between viral- and cell-coded proteins could be involved in determining some of the observed transformation-related cellular phenotypic changes is discussed. (73 Refs)

41. CELL SURFACE ALTERATIONS ASSOCIATED WITH TRANSFORMATION AND TUMORIGENICITY IN HUMAN CELLS.

Der CJ
University of California, Irvine, CA
Diss Abstr Int [B]; 42(9):3573-B 1982

The model system utilized for these studies consisted of a series of HeLa/fibroblast hybrids. Although these hybrids continued to express a transformed phenotype in culture, they were completely suppressed for tumorigenicity. From these suppressed hybrid populations, rare tumorigenic segregant subpopulations arose which had regained tumorigenic potential. The relationship between fibronectin expression and tumorigenicity was evaluated in these genetically similar nontumorigenic and tumorigenic hybrids. Quantitation of surface fibronectin expression by immunofluorescence and by SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis) of iodinated cell surface proteins demonstrated on correlation between the decreased level of fibronectin and tumorigenicity. The relationship between cytoskeletal organization and tumorigenicity was analyzed by immunofluorescence. Complex microtubule organization was found in all cells, independent of tumorigenicity. Although disorganized microfilaments were observed in tumorigenic hybrids, the organization of microfilaments was found to be related to cellular morphology and not tumorigenic potential. Double stain immunofluorescence demonstrated a close relationship between surface fibronectin and cytoplasmic microfilaments. Finally, the antigenic profiles of the hybrids were evaluated by utilizing antisera generated against either live nontumorigenic or tumorigenic hybrids. By immunofluorescence and immunoprecipitation analysis, no unique nontumorigenic hybrid antigens were identified. However, a single cell surface antigen of molecular weight 75,000 (75K protein) was identified that correlated exclusively with tumorigenicity. The 75K protein was not synthesized in fibroblasts or nontumorigenic hybrids and represented only 0.03% of the total cellular protein in HeLa and tumorigenic hybrids. Radiolabeling studies demonstrated its glycosylated nature and identified the 75K protein as a phosphoprotein. (no Refs)

42. CHARACTERIZATION OF AN ANTIGEN ASSOCIATED WITH THE MAREK'S DISEASE LYMPHOBLASTOID CELL LINE MSB-1.

Ross LJ
Houghton Poultry Res. Station, Huntingdon, Cambs. PE172DA, England
J Gen Virol; 60(part2):375-380 1982

A Marek's disease lymphoblastoid cell line (MSB-1) has been analyzed by immunoprecipitation for expression of tumor-associated antigen, Marek's disease virus (MDV)-specific antigens and antigens specific to avian leukosis-sarcoma viruses. Rabbit antisera raised against two independently derived cell lines after extensive absorption with normal chick cells reacted with a polypeptide of mol wt 40,000 (40K) in extracts of MSB-1 cells. The 40K polypeptide was not present in myeloblasts or in chick embryo fibroblasts (CEF) infected with MDV and did not react with antiserum raised against normal chicken thymus antigens. The possibility that the 40K polypeptide is a tumor-associated antigen is discussed. Seven MDV-specific antigens were noted in infected CEF (mol wt 110K, 100K, 80K, 70K, 50K, 35K and 32K) but none of these was detected in MSB-1 cells. The avian leukosis-sarcoma group-specific antigen P27gag and its precursor Pr76gag were not found in MSB-1 cells, confirming that expression of mature gag protein is not required for transformation by MDV. However, two polypeptides of unknown origin and function (mol wt 180K and 110K) were precipitated from MSB-1 cells with a rabbit anti-Rous sarcoma (Schmidt-Rupin, subgroup D) antiserum. (Author abstract) (17 Refs)

43. IMMUNOLOGICAL CHARACTERIZATION OF MAREK'S DISEASE LYMPHOID TUMOR CELLS.

Slaght SS
The University of Connecticut, Storrs, CT
Diss Abstr Int [B]; 42(9):3629-B 1982

Analyses of the tumor-cell lines GBT and MSB-1, as well as a Marek's disease-derived leukemia population for lymphocyte markers, showed no similarities to thymus or bursa cells, nor to the thymus-derived or bursa-derived peripheral blood T- and B-cells. Since phagocytic activity and Ig-Fc region binding were also absent, the tumor cells were assigned to the category of null cells. Tests for tumor-associated antigens revealed the presence of a multiplicity of such antigens. Different passages of the GBT cell line were shown to express different relative concentrations of tumor-associated antigens, as were Marek's disease tumor cells from other sources. It was concluded that more than one antigen was expressed by a single GBT cell and that different cells transformed by the same virus were expressing either different antigens or a few in different proportions. It was suggested that more than one target cell-type exists for the viral transformation. (no Refs)

MORPHOLOGICAL AND OTHER BIOLOGICAL ASPECTS OF ONCOGENIC TRANSFORMATION

44. GROWTH CONTROL MEDIATED BY THE COUPLING OF GROWTH ARREST AND DIFFERENTIATION: DEFECTS IN MALIGNANT CELLS (MEETING ABSTRACT).

Scott RE, Hoerl BJ, Wille JJ, Maercklein PB
Section of Experimental Pathology, Mayo Clinic/Foundation, Rochester, MN
Fed Proc; 41(3):489 1982

Cell proliferation in vivo can be regulated by the coupling of G1 growth arrest and differentiation. The mechanisms which control these processes are however poorly understood because most in vitro studies have been performed on cell lines which lack the capacity to differentiate. We have therefore studied 3T3 T proadipocytes because: 1) they are nontransformed and noninitiated cells, 2) they can differentiate under physiological conditions, and 3) they can regulate their proliferation by the coupling of growth arrest and differentiation. Five distinct phases are now shown to be involved in the coupling process. First, cells must growth arrest at a distinct state in the G1 phase of the cell cycle, designated GD (phase 1). GD arrested cells can then either be stimulated to grow or to differentiate. Cells first nonterminally differentiate (phase 2), then they either terminally differentiate (phase 3) or they loose the differentiated phenotype (phase 4) and reinitiate proliferation (phase 5). Studies on 32 noncloned and 8 cloned tumorigenic proadipocyte cell lines established that malignant transformation prevents the differentiation of proadipocytes by blocking their capacity to GD arrest. We therefore suggest that defective coupling of growth arrest and differentiation may be of etiological significance in the pathogenesis of neoplasia. (no Refs)

45. NUCLEAR LOCATION OF THE PUTATIVE TRANSFORMING PROTEIN OF AVIAN MYELOCYTOMATOSIS VIRUS.

Abrams HD, Rohrschneider LR, Eisenman RN
Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
Cell; 29(2):427-439 1982

The putative transforming protein of avian myelocytomatosis virus MC29 is a 110,000 dalton (P110gag-myc) polyprotein comprised of sequences derived from both the gag region and the MC29-specific myc region. Two approaches have been taken to determine the location of the MC29 gag-related proteins in transformed cells: subcellular fractionation and immunofluorescence. Analysis of subcellular fractions of MC29-transformed cells by immunoprecipitation indicates that the majority of the gag-myc polyprotein is found in the nuclear fractions of Q8 cells (a nonproducer line of MC29-transformed quail embryo fibroblasts) and nonproducer cells derived from a liver tumor of MC29-infected quail. This is in contrast to the distribution of gag-related helper virus proteins lacking myc, which are found only in nonnuclear fractions of superinfected Q8 cells. The purity of unlabeled nuclei was assessed by electron microscopy and enzyme assays, revealing little contaminating material from other subcellular fractions. Immunofluorescence experiments using monospecific anti-gag serum showed specific, intense immunofluorescence in the nuclei of fixed Q8 cells. In contrast, the majority of P75gag-erb, a candidate transforming protein produced by avian erythroblastosis virus (AEV), is absent from the nuclei of nonproducer AEV-transformed chick embryo fibroblasts. The nuclear association of the MC29 transforming protein may be related to some of the unique properties of MC29-transformed cells. (Author abstract) (68 Refs)

46. RELATIONSHIP BETWEEN ANCHORAGE-INDEPENDENT GROWTH AND CYTOCHALASIN B-INDUCED MULTINUCLEATION IN CLONED BHK-21/C13 CELLS AND THEIR CHEMICAL TRANSFORMANTS.

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Cell Struct Funct; 7(1):61-70 1982

Clones of BHK-21 cells derived from flat colonies, that were selected for their extremely low growth on agar plates (Ag-clones) had low cytochalasin B (CB)-multinucleated cell rates (CB-MCR), whereas parent BHK-21 cells could grow on an agar plate and had high CB-MCR. Many transformants induced in an Ag- clone (L77), after treatment with N-methyl-N'-nitro-N-nitrosoguanidine, retained their ability to grow on an agar plate and most showed increased CB-MCR. The study indicates that anchorage-independent growth and CB-multinucleation are closely related, and that both can be induced simultaneously during chemical transformation. (29 Refs)

47. SEQUENTIAL CHANGES IN DIPLOID RAT LIVER EPITHELIAL CELLS TREATED WITH AFLATOXIN B1 IN CULTURE (MEETING ABSTRACT).

Iype PT, Currens MJ, Herring A, Kelley SP, McMahon JB, Ray-Chaudhuri R, Malan-Shibley L

National Cancer Institute-Frederick Cancer Research Facility, Frederick, MD, 21701

Proc Am Assoc Cancer Res; 23:290 1982

Experiments were performed to analyze the chronology of the onset of transformation markers induced in rat liver cells by the hepatocarcinogen, aflatoxin B1 (AFL). A well-characterized, diploid liver epithelial cell line which exhibited no transformation markers was used at the tenth subculture. Three groups were studied. Group 1 consisted of untreated cells, Group 2, cells receiving a single treatment, and Group 3 cells given multiple exposures to the compound. The markers followed included altered karyology, loss of response to an hepatic proliferation-regulating protein (HPI), induced multinucleation by cytochalasin B, the presence of gamma-glutamyl transpeptidase (gamma-GT) and alpha-fetoprotein, the ability to bind concanavalin A coupled with agarose beads, the formation of colonies in soft agarose, and the growth of tumors in rats. Group 1 exhibited none of these characteristics for the 34 week duration of the study, except that aneuploid cells were seen in the population at 23 weeks. The earliest change seen in Groups 2 and 3 was a shift to a hyperdiploid karyology and the occurrence of marker chromosomes, which was followed by a loss of response to HPI, expression of gamma-GT, induction of multinucleation, growth in soft agar and tumorigenicity. Markers were observed at an earlier time in Group 3 compared with Group 2. The sequential appearance of these different markers might be indicative of progressive changes leading to malignancy. (no Refs)

48. POSSIBLE IMMUNOLOGICAL MECHANISMS IN C-TYPE VIRAL LEUKEMOGENESIS IN MICE.

Ihle JN, Lee JC

Biological Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD

Curr Top Microbiol Immunol; 98:85-101 1982

The role of C-type viruses in leukemogenesis in mice is reviewed. The mechanisms by which C-type viruses induce leukemia are distinct from those by which the same type of viruses induce sarcomas. In leukemogenesis the viruses are replication-competent, nontransforming, and do not contain additional cellular pathogenic sequences. Latency periods are longer for leukemia than for sarcomas. Induction of leukemia is associated with acute viremia. Studies in mice indicate cellular immune response is an integral part of the process of leukemogenesis. Among the specific components of the leukemogenic process is the absolute requirement for antigen-specific lymphocytes. Preleukemic states involve chronic immune stimulation that is not limited to antigen-specific components but includes systemic effects. A proposed model suggests that immune stimulation is required to provide targets for viral infection and transformation. A second model describes a unique interaction of virus with antigen-specific cells to produce transformation. In a third proposed model, chronic immune stimulation produces somatic errors, which result in transformation leading to leukemia. Experimental approaches are available for future research to clarify the mechanisms of viral leukemogenesis. (63 Refs)

49. CYCLIC AMP INDUCES TS-ALTERATIONS IN MORPHOLOGY IN RAT LIVER EPITHELIAL CELL TS-TRANSFORMANTS (MEETING ABSTRACT).

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Department of Biochemistry, Boston University School of Medicine, Boston, MA, 02118

Proc Am Assoc Cancer Res; 23:102 1982

Cholera toxin via its ability to increase intracellular cyclic AMP levels can induce drastic changes in cell morphology. We have found that a rat liver epithelial cell (TS-223) which is ts for expression of certain transformed properties is also ts for cyclic AMP-induced morphological alterations. TS-223 cells were treated with various concentrations of cholera toxin (CT) or 8-bromocyclic AMP (8BrcA) at either the permissive temperature (37C) or the non-permissive temperature (40.5C). Following a 2-5 hr incubation period, the cells were photographed and processed for cyclic AMP measurements. Both CT and 8BrcA only altered cell shape at the permissive temperature. These changes consisted of extensive cytoplasmic process formation and occasional rounding of the cell body. Shift-up/shift-down experiments indicated that the change in the response occurred rapidly ie within 2 hrs. Cyclic AMP measurements indicated that CT stimulated cyclic AMP production to the same extent at either temperature. Cycloheximide at concentrations which inhibited protein synthesis by 80% did not prevent the acquisition of responsiveness during shift-down experiments. The data suggest the presence of either ts-sensitive cyclic AMP-dependent protein kinases or phosphate-acceptor protein substrates. (no Refs)

50. INDUCTION OF A TRANSFORMING AGENT(S) BY ABORTIVE INFECTION OF HERPES SIMPLEX VIRUS IN THE CELLS CARRYING ENDOGENOUS SARCOMA VIRUS.

Shimizu Y, Kumagai K
Dept. Microbiology, Tohoku Univ. Sch. Dentistry, Sendai, Japan
Excerpta Med Int Congr Ser; 571:29-33 1982

Abortive infection of herpes simplex virus Type 2 (HSV-2) in the murine and hamster cell lines carrying endogenous sarcoma virus induces an agent(s) with in vitro transforming activity in the culture fluids. Two transformed lines positive for murine sarcoma virus but negative for murine leukemia virus were used: D-56 cells derived from murine cell line NIH 3T3, and HT-1 cells derived from a hamster tumor. Normal NIH 3T3 and baby hamster kidney cells and the transformed cells were infected with HSV-2. No increase of virus progeny was seen with either D-56 or HT-1 cells. After cultivation at 37 C for 1 day, the culture fluids were examined for transforming activity using 3T3 or mouse embryo cells which had been treated with diethylaminoethanol-dextran. The exposed cells were subcultured and tested for the appearance of transformed foci in soft agar medium. After 3-4 wk, 2-3 transformed foci/dish appeared only in the 3T3 cell cultures treated with the culture fluids of infected D-56 cells. No foci could be seen with either infected or uninfected 3T3 cells. These results indicate the HSV-2 was not able to replicate in D-56 cells, but did induce an agent(s) with transforming activity in the culture fluids. The possible nature of the agent(s) is discussed. (9 Refs)

51. ROUS SARCOMA VIRUS TRANSFORM HUMAN NORMAL FIBROBLASTS AND 'SUPERTRANSFORM' HUMAN SARCOMA CELLS (MEETING ABSTRACT).

Rabotti G, Teutsch B, Mongiat F, Mariller M
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Proc Am Assoc Cancer Res; 23:99 1982

Sixty cell lines of human fibroblasts originating from 60 different donors were infected with various strains of Rous Sarcoma Virus (RSV). Two cell lines were successfully transformed. This was achieved with one strain of virus only: Schmidt-Ruppin RSV (Sr RSV subgroup B). The virus was recovered upon co-cultivation of the transformed cells with susceptible chicken fibroblasts (CEF). Suprisingly these cells were found to produce viral particles as demonstrated by infectivity assays of filtered supernatant. The avian transforming virus produced by human cells has the typical type C morphology and some of the antigenic proteins of RSV. Cell-lines of undifferentiated sarcomas originating from 6 different patients were also infected with the same strains of RSV. One cell line was successfully 'supertransformed' it was virogenic (upon co-cultivation with CEF) and produced infectious virus. This is the first demonstration of transformation of human normal fibroblasts by an avian retrovirus. The data showing that only 2 out of 60 cell phenotypes and 1 out of 6 sarcoma cell lines were transformed suggest that susceptibility to RSV transformation in human cells is genetically controlled. Since in their natural hosts these viruses are known to recombine with cellular information it is possible that a similar event takes place here and that recombination of RSV with human cellular sequences may occur in this virus produced in human cells. (no Refs)

52. MORPHOLOGICAL EVIDENCE FOR CYCLIC AMP-INDUCED REVERSE TRANSFORMATION IN VOLE CELLS INFECTED WITH AVIAN SARCOMA VIRUS.

Meek WD
Univ. Colorado Health Science Center, Denver, CO, 80262
Mol Cell Biol; 2(7):863-874 1982

Ultrastructural changes that result from dibutyryl cyclic AMP treatment were studied in vole cells. Scanning electron microscopy of the avian sarcoma virus-transformed cells showed the spherical cells covered with microvilli. Filopodia like those seen on mitotic normal cells radiated from the cell body. With fluorescent phalloidin, a rim of actin was noted below the cell membrane of the spherical cells. With an increasing concentration of reverse transformation (RT) agent, more cells became flattended and resembled the normal fibroblasts. Coating the substrate with polylysine did not affect the transformed cell shape when grown in normal medium, but the coated substrate increased the RT response. The ruffling that was common to normal cells occurred in some RT cells, but most cells had rigid, smooth borders. Transmission electron microscopy confirmed the results seen with antitubulin indirect immunofluorescence and the present results with fluorescent phalloidin and antiactin: long tubules ran parallel to the subplasmalemmal microfilament bundles, and intermediate filaments were parallel to the other microfibrils and prevalent in slender processes. Fibronectin was absent on the surface of the transformed vole cell. The long strands which extende from cell to cell in normal cultures were also absent. However, in the RT vole cell, short fibronectin fibrils appeared along the cell periphery. (47 Refs)

53. PHENOTYPIC DIFFERENCES BETWEEN TUMOR CELLS DERIVED FROM DIFFERENT STAGES OF NEOPLASTIC GROWTH.

Wainberg MA, Germinario RJ
Lady Davis Inst Medical Res., Sir Mortimer B. Davis-Jewish General Hosp., Montreal, Quebec, Canada
Eur J Cancer Clin Oncol; 18(6):545-551 1982

Under conditions employed in our laboratory, tumors which are induced by avian sarcoma virus (ASV) usually grow progressively for several weeks and then regress. In order to further understand the basis for tumor regression in this model, we compared avian sarcoma cells which were cultured from tumors at different stages of development in terms of various phenotypic properties. The results indicate that tumor cells which are derived from progressively-growing sarcomas are rapidly growing, produce large quantities of the enzyme plasminogen activator, and have much in common generally with chicken embryo fibroblast (CEF) cells that have been transformed by ASV. In contrast, tumor cells that are obtained from regressors have elevated levels of hexose transport, grow very slowly, are greatly enlarged and display properties that are characteristic of senescent cells in culture. (Author abstract) (19 Refs)

ASSAYS OF ONCOGENIC TRANSFORMATION

54. A METHOD FOR AMPLIFICATION OF SENSITIVITY OF THE C3H 10T 1/2 CELL TRANSFORMATION ASSAY (MEETING ABSTRACT).

Schechtman LM, Kiss E, McCarvill J, Gallagher M, Kouri RE, Lubet RA
Microbiological Associates, Bethesda, MD, 20816
Proc Am Assoc Cancer Res; 23:289 1982

Although the 10T 1/2 cells have been shown to be sensitive to a variety of chemical carcinogens, not all genotoxins can be detected using the standard transformation assay of Heidelberger and coworkers. Assay modifications, eg cell synchronization have been found necessary in certain instances to yield the expected response. In order to enhance its sensitivity we have modified the standard 10T 1/2 ('Level I') assay by a procedure designated 'Level II Amplification,' wherein target cells are replated at various times post-treatment for expression of phenotypic transformation. The technique is applicable both in the absence and presence of metabolic supplements, and does not require cell synchronization. It permits amplification of chemically transformed cells which might otherwise go undetected in the originally treated cell population. This procedure has resulted in detectable transformation of 10T 1/2 cells by chemical classes such as alkylating agents (eg N-methyl-N'-nitro-N-nitrosoguanidine), aromatic amines (eg 2-acetyl aminofluorene), nitrosamines (eg diethylnitrosamine), and polycyclic hydrocarbons (eg dibenz(a,h)anthracene), which induce little or no Level I response. Detectable focus transformation is specific for carcinogenic chemicals. No response was observed among untreated cells or those exposed to the non-carcinogens phenanthrene and anthracene, or to solvent vehicles (eg acetone). Moreover, chemicals inducing a Level I response continued to yield a Level II response. (2 Refs)

55. IMPROVED TRANSFORMATION OF C3H10T1/2CL8 CELLS BY DIRECT-AND INDIRECT-ACTING CARCINOGENS (MEETING ABSTRACT).

Nesnow S, Garland H, Curtis G
Carcinogenesis and Metabolism Branch, US Environmental Protection Agency, Research Triangle Park, NC, 27711
Proc Am Assoc Cancer Res; 23:284 1982

C3H10T1/2CL8 cells are transformed by a variety of structurally different chemicals, including polycyclic aromatic hydrocarbons, aromatic amines, and pyrimidines. It has been reported that C3H10T1/2CL8 cells are insensitive to the transforming effects of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) unless the cells are synchronized. This finding is particularly interesting because MNNG mutates C3H10T1/2CL8 cells to ouabain resistance without the need for cell synchrony. Aflatoxin B1 (AFB1) also does not transform C3H10T1/2CL8 cells under conditions described by Reznikoff et al. We report here that oncogenic transformation of C3H10T1/2CL8 cells can be improved by treating asynchronous cultures of cells 5 days after seeding. Benzo(a)pyrene-induced transformation was increased fourfold by this method, compared with treating the cells 1 day after seeding. MNNG produced an average of 1 focus/dish, with 61% of the dishes exhibiting foci, when administered 5 days after seeding. Propane sultone and AFB1 also produced marked transformation responses when administered 5 days after seeding. However, 4-dimethylaminoazobenzene and urethane did not induce transformation when administered either 1 day or 5 days after seeding. With all chemicals examined, clonal cytotoxicity was reduced when they were administered 5 days after seeding. (1 Ref)

56. DETECTION OF CARCINOGENS WHICH INITIATE THE PROCESS OF C3H/10T1/2 CELL TRANSFORMATION (MEETING ABSTRACT).

Boreiko CJ, Abernethy DJ, Frazelle JH
Chemical Industry Institute of Toxicology, Research Triangle Park, NC, 27709
Proc Am Assoc Cancer Res; 23:285 1982

It is known that Formaldehyde, N-methyl-N'-nitro-N-nitrosoguanidine and aflatoxin B1 initiate the process of C3H/10T1/2 transformation, producing transformed foci only when treated cells are subsequently exposed to the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA). Studies were conducted to establish whether initiation of transformation is a common consequence of exposure to chemical carcinogens. Cell culture conditions optimal for the detection of initiating agents were determined and the ability of carcinogens to transform or initiate transformation examined. Treatment with cytotoxic concentrations of N-nitrosomethylurea, N-nitrosoethylurea, methylmethanesulfonate and ethylmethanesulfonate followed by continuous exposure to 0.25 ug/ml TPA produced foci in at least 25% of the dishes exposed to the highest concentration of each compound. Foci were generally not observed in dishes exposed to TPA alone or in chemically treated dishes not exposed to TPA. Mitomycin C, 5-fluorodeoxyuridine, amethopterin and 5-azacytidine, alone produced foci in 4-47% of treated dishes and exposure to TPA enhanced focus frequency more than two-fold. In the absence of TPA, 3-methylcholanthrene and benzo(a)pyrene produced foci in 50-100% of treated dishes. TPA caused 50% and 22% reductions in focus formation by 3-methylcholanthrene and benzo(a)pyrene respectively. These studies indicate that some classes of carcinogens function as initiating agents in the standard C3H/10T1/2 transformation protocol and that the presence of TPA can significantly enhance the sensitivity of this system to genotoxic substances. (no Refs)

57. INDUCTION OF NEOPLASTIC TRANSFORMATION AND SINGLE STRAND DNA BREAKS IN C3H 10T1/2 CELLS BY POLYCYCLIC HYDROCARBONS AND SHORT CHAIN ALKYLATING AGENTS (MEETING ABSTRACT).

Schechtman LM, Gallagher MA, Henry CJ, Kouri RE, Lubet RA
Microbiological Associates, Bethesda, MD, 20816
Fed Proc; 41(3):379 1982

The known carcinogens benzo(a)pyrene, BaP 7,8-diol, 3-methylcholanthrene, and 7,12-dimethyl benz(a)anthracene, all yielded striking dose-dependent transformation frequencies when tested in the standard 10T1/2 assay. In contrast, the two non-carcinogens anthracene and phenanthrene caused no transformation. The strong chemical carcinogen, dibenz(a,h)anthracene expressed weak transforming activity, while the weak carcinogen, benzo(e)pyrene expressed stronger activity. The short chain alkylating agents N-methyl-N'-nitro-N-nitrosoguanidine and ethyl methanesulfonate induced minimal transformation in the standard 10T 1/2 assay. However, it appears that modification of the assay by replating treated cells post-chemical treatment enhances the ability of the system to identify the short chain alkylating agents. We attempted to optimize carcinogen exposure employing a modified alkaline elution assay (which measures the production of single strand breaks). This test demonstrated few if any DNA strand breaks upon treament with transforming doses of BaP, or BaP-7,8-diol, whereas significant levels of strand breakage were observed following treatment with minimally toxic non-transforming doses of a number of short chain alkylating agents. (no Refs)

58. A COMPARISON OF EXPRESSION OF NEOPLASTIC POTENTIAL OF CARCINOGEN-TRANSFORMED HUMAN FIBROBLASTS IN NUDE MICE AND IN CHICK EMBRYONIC SKIN.

Donahoe J, Noyes I, Milo GE, Weisbrode SE
Comprehensive Cancer Center, Suite 302, 410 W. 12th Ave., Columbus, OH, 43210
In Vitro; 18(5):429-434 1982

Human foreskin fibroblasts transformed by representative chemicals from five different classes of chemical carcinogens, some requiring enzymatic activation and direct acting carcinogens, produced cell populations that exhibited anchorage-independent growth and expression of neoplastic potential in either nude mice or chick-embryonic skin (CES). There is a high degree of correlation between tumor incidence and invasiveness of CES. The unique feature of CES is the rapidity of expression of cellular neoplasia and interpretation of the simulated tumor in 4 d as a simulated fibrosarcoma. This method represents a system that can be used to evaluate human carcinogens in vitro in 6 to 10 wk. (Author abstract) (11 Refs)

GENERAL REVIEWS AND OTHER RELATED STUDIES

59. THE TRANSFORMED CELL.

Cameron IL, Pool TB
Dept. Anatomy, Univ. Texas Health Science Center at San Antonio, San Antonio, TX, 78284
The Transformed Cell. New York, Academic Press, 435 pp., 1981.

Differences between normal and neoplastic transformed cells are described. Topics discussed include a brief description of terminology and basic concepts; background material related to evidence for and against the possible correlation of in vivo tumorigenicity to in vitro changes in the cytoskeletal system, anchorage-dependent growth, plasminogen activator production, agglutinability by lectins, and cell surface and plasma membrane properties; general aspects of regulation of cell proliferation and the relationships between ion movement and energy metabolism in normal and transformed cells; viral transformation of cells; and selected cellular properties, including cyclic nucleotides, polyamine metabolism, mobility of cellular water, cell viscosity, intracellular pH, and element concentration. (1490 Refs)

60. BIOLOGICAL CARCINOGENESIS.

Rich MA, Furmanski F
AMC Cancer Res. Center and Hosp., Lakewood, CO
Biological Carcinogenesis. New York, Marcel Dekker, Inc., 310 pp., 1982.

The general principles which govern carcinogenesis are identified for each of the major classes of carcinogens and the extent these principles are applicable to the carcinogenic process induced by other classes of agents is determined. Current knowledge on the interaction of carcinogens and the identification of biological systems where viral, chemical, and physical carcinogens are demonstrably interactive are described. Mechanisms in viral carcinogenesis are discussed with respect to: T-cell growth, T-cell growth factor, T-cell leukemias and lymphomas and isolation of a new type-C retrovirus, properties of sarcoma growth factors produced by sarcoma virus transformed cells, and interactions of murine leukemia viruses with hematopoietic stem cells. Mechanisms in chemical carcinogenesis are discussed with respect to activation of carcinogenic polycyclic hydrocarbons by metabolism, involvement of a protein kinase in multistage skin tumor promotion, and the effect of tumor-causing chemicals on the control of mutagenesis and differentiation in mammalian cells. Transformation of cloned mammary epithelial cells following combined treatment with mouse mammary tumor virus and dimethylbenz(a)anthracene, virus-cell interactions during hormonal carcinogenesis, and separate pathways for viral and chemical carcinogenesis in the mouse mammary gland are described. A molecular approach to studies of chemical carcinogen-virus interaction is presented. Other presentations deal with multistage recombinational origin of leukemogenic viruses, radiation-induced leukemogenesis, neoplastic transformation of cultured cells by herpes simplex virus type 2 and carcinogens, modulation of adenovirus transformation and replication, and transformation of murine fibroblasts. (682 Refs)

61. AVIAN LEUKEMIA VIRUSES ONCOGENESES AND GENOME STRUCTURE.

Graf T, Stehelin D
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Biochim Biophys Acta; 651(4):245-271 1982

Avian leukemia viruses, with emphasis mainly on defective leukemia viruses (DLVs), are reviewed. Oncogenic spectra of chicken-derived DLVs and the turkey-derived reticuloendotheliosis virus (REVT) are presented. Transformation specificity of DLVs in vitro, genetic content and genome structure of avian erythroblastosis virus (AEV), avian myeloblastosis virus (AMV)-type, myelocytomatosis virus strain 29 (MC29)-type, REVT, expression of RNA and proteins in cells infected with AEV, AMV, MC29, and OK10, genetics of DLVs including mutants in transforming functions and recovered viruses, conservation of cellular oncogene (c-onc) genes through evolution, chromosomal localization and structure of c-onc genes, and expression of c-onc genes in normal cells, mechanisms of transformation by avian leukosis viruses (ALV) and DLVs, the promoter insertion hypothesis of ALV-leukemogenesis, hematopoietic target cell specificity and possible role of c-onc genes in the DLV-leukemogenesis, and transformation of nonhematopoietic cells by DLVs are discussed. Origin of DLVs is reviewed, including reverse transcription of encapsidated viral and cellular RNAs, viral promoter insertion, recombination of integrated provirus with a c-onc gene, and integration of proviruses around a c-onc gene. (167 Refs)

62. HYPERPLASTIC AND NEOPLASTIC ERYTHROPROLIFERATIVE DISEASES INDUCED BY ONCOGENIC MURINE RETROVIRUSES.

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Biochim Biophys Acta; 651(4):273-283 1982

Structure of Harvey (HV) and Kirsten virus (KV), transforming protein of HV and KV, and Friend virus complex are discussed. Comparison of polycythemia- and anemia-inducing strains of spleen focus-forming virus (SFFV) is presented. Friend murine leukemia virus-induced (F-MuLV) disease and pathophysiology of F-MuLV-induced disease are described. Possible pathophysiological relationships between Friend virus-induced erythoproliferation and Harvey sarcoma virus (HaSV)-induced erythroleukemia are discussed. Biochemistry of transforming proteins of erythroleukemia viruses is reviewed. One possible advantage that studies of erythroleukemia have is that the abnormal proliferation of erythroid precursor cells induced by SFFV or Ha-SV is accompanied by a decreased requirement by these cells for erythropoietin. Studies on erythroid cells are limited by the availability of large quantities of purified erythropoietin. Both polycythemia-inducing SFFV and Ha-SV induce the abnormal proliferation of fully hemoglobinized erythroid colonies in cell culture colony assays for the viruses. Results might suggest that Ha-SV infection of stem cells could be a method for generating stem cell lines. (81 Refs)

63. ROLE OF ENZYMATIC METHYLATION OF DNA IN CELL DIFFERENTIATION AND TRANSFORMATION.

Fedorov NA
Central Res. Inst. Hematology and Blood Transfusion, Moscow, USSR
Eksp Onkol; 4(3):3-11 1982

Literature data on DNA methylation are reviewed, with special emphasis on the roles of specific DNA methylases and S-adenosylmethionine (SAM) in cell differentiation and neoplastic transformation. Determinations of 5-methylcytosine contents of leukemic and normal lymphocytes showed a marked elevation of DNA methylation in the leukemic cells. Changes in rate and specificity of DNA methylation were observed during chemical carcinogenesis and following administration of antineoplastic agents. A number of SAM analogs were shown to inhibit cell proliferation. (73 Refs) (In RUS)

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CHEMICAL CARCINOGENESIS

1. ASBESTOS CARCINOGENESIS: ASBESTOS INTERACTIONS AND EPITHELIAL LESIONS IN CULTURED HUMAN TRACHEOBRONCHIAL TISSUES AND CELLS.
Haugen A, Harris C
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Dept. Obstetrics and Gynecology, Hadassah Univ. Hosp., POB 12000, 91120 Jerusalem, Israel
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The Work of the NRPB 1977/80 and a Review of the First 10 Years. Chilton, Didcot, Oxfordshire, National Radiological Protection Board, 70 pp., 1981.

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6. ZINC, COPPER, AND MANGANESE IN IMMUNE FUNCTION AND EXPERIMENTAL ONCOGENESIS.
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